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(54) INHIBITORS OF FACTOR XA WITH A NEUTRAL P1 SPECIFICITY GROUP

INHIBITOREN DES FAKTORS XA MIT EINER NEUTRALEN GRUPPE MIT P1-SPEZIFITÄT

INHIBITEURS DU FACTEUR Xa COMPRENANT UN GROUPE A SPECIFICITE P1 NEUTRE

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WO-A-95/18111	**WO-A-96/28427**
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US-A- 4 226 877	**US-A- 5 262 412**
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Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

EP 0 991 625 B1

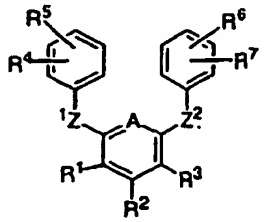
Description

FIELD OF THE INVENTION

[0001] This invention relates generally to novel inhibitors of factor Xa with a neutral P1 specificity group, pharmaceutical compositions containing the same, the same for use in therapy, and the use of the same for the manufacture of a medicament for the treatment of thromboembolic disorders.

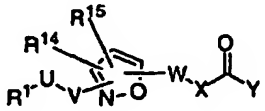
BACKGROUND OF THE INVENTION

[0002] WO 96/28427 describes benzamidine anticoagulants of the formula:



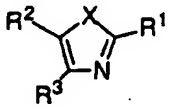
wherein Z^1 and Z^2 are O, N(R), S or OCH_2 and the central ring may be phenyl or a variety of heterocycles. The presently claimed compounds do not contain the Z^1 linker or the .substitution pattern of the above compounds.

[0003] WO 95/13155 and PCT International Application US 96/07692 describe isoxazoline and isoxazole fibrinogen receptor antagonists of the formula:



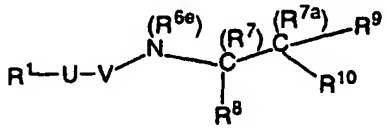
wherein R^1 may be a basic group, U-V may be a six-membered aromatic ring, W-X may be a variety of linear or cyclic groups, and Y is an oxy group. Thus, these compounds all contain an acid functionality (i.e., W-X-C(=O)-Y). In contrast, the presently claimed compounds do not contain such an acid functionality.

[0004] EP 0,513,387 depicts active oxygen inhibitors which are oxazoles or thiazoles of the formula:



wherein X is O or S, R^2 is preferably hydrogen, and both R^1 and R^3 are substituted cyclic groups, with at least one being phenyl. The presently claimed invention does not relate to these types of oxazoles or thiazoles.

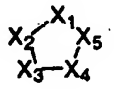
[0005] WO 95/18111 addresses fibrinogen receptor antagonists, containing basic and acidic termini, of the formula:



wherein R^1 represents the basic termini, U is an alkylene or heteroatom linker, V may be a heterocycle, and the right

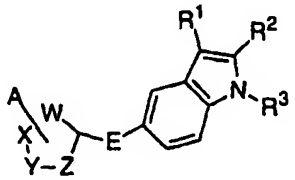
hand portion of the molecule represents the acidic termini. The presently claimed compounds do not contain the acidic or basic termini of WO 95/18111.

[0006] In U.S. Patent No. 5,463,071, Himmelsbach et al depict cell aggregation inhibitors which are 5-membered heterocycles of the formula:



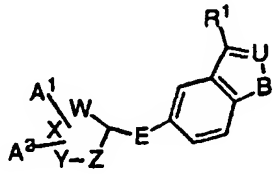
wherein the heterocycle may be aromatic and groups A-B-C-and F-E-D-are attached to the ring system. A-B-C-can be a wide variety of substituents including a basic group attached to an aromatic ring. The F-E-D-group, however, would appear to be an acidic functionality which differs from the present invention. Furthermore, use of these compounds as inhibitors of factor Xa is not discussed.

[0007] Baker et al, in U.S. Patent No. 5,317,103, discuss 5-HT_1 agonists which are indole substituted five-membered heteroaromatic compounds of the formula:



wherein R^1 may be pyrrolidine or piperidine and A may be a basic group including amino and amidino. Baker et al, however, do not indicate that A can be a substituted ring system like that contained in the presently claimed heteroaromatics.

[0008] Baker et al, in WO 94/02477, discuss 5-HT_1 agonists which are imidazoles, triazoles, or tetrazoles of the formula:

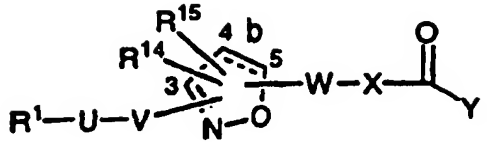


wherein R^1 represents a nitrogen containing ring system or a nitrogen substituted cyclobutane, and A may be a basic group including amino and amidino. But, Baker et al do not indicate that A can be a substituted ring system like that contained in the presently claimed heteroaromatics.

[0009] Tidwell et al, in *J. Med. Chem.* **1978**, *21(7)*, 613-623, describe a series of diarylamidine derivatives including 3,5-bis(4-amidinophenyl)isoxazole. This series of compounds was tested against thrombin, trypsin, and pancreatic kallikrein. The presently claimed invention does not include these types of compounds.

[0010] Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V, Ca^{2+} and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin (Elodi, S. Varadi, K.: *Optimization of conditions for the catalytic effect of the factor IXa-factor VIII Complex: Probable role of the complex in the amplification of blood coagulation. Thromb. Res.* **1979**, *15*, 617-629), inhibition of factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system.

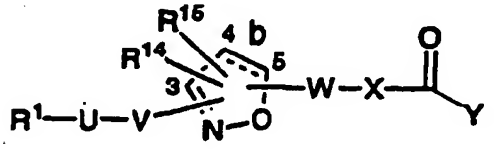
[0011] WO 95/14683 and WO 96/38426 describe nonpeptide compounds of formula A:



(A)

which bind to integrin receptors thereby altering cell-matrix and cell-cell adhesion properties.

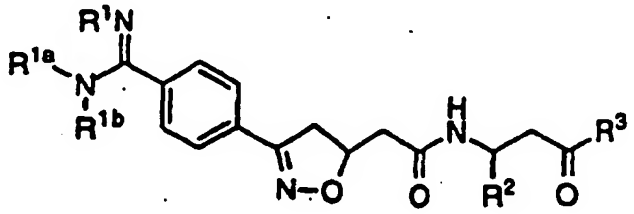
[0012] WO 96/37482 describes nonpeptide compounds of formula B:



(B)

which bind to integrin receptors thereby altering cell-matrix and cell-cell adhesion processes.

[0013] WO 95/14682 and US 5,446,056 describe compounds of formula C:



(C)

which are useful as antagonists of the platelet glycoprotein IIb/IIIa complex.

[0014] Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors.

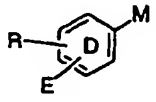
SUMMARY OF THE INVENTION

[0015] Accordingly, one object of the present invention is to provide novel inhibitors of factor Xa with a neutral P1 specificity group or pharmaceutically acceptable salts thereof.

[0016] It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt form thereof.

[0017] It is another object of the present invention to provide compounds of the present invention or a pharmaceutically acceptable salt form thereof for use in treating thromboembolic disorders.

[0018] These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula (I):



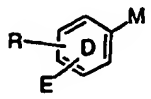
I

or pharmaceutically acceptable salt forms thereof, wherein D, E, M, and R are defined below, are effective factor Xa inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in a first embodiment, the present invention provides novel compounds of formula I:

[0019]



I

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein:

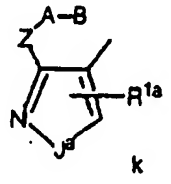
ring D is phenyl or pyridyl:

E is selected from F, Cl, Br, I, OH, C_{1-3} alkoxy, SH, C_{1-3} alkyl-S, $S(O)R^{3b}$, $S(O)_2R^{3a}$, $S(O)_2NR^2R^{2a}$, and OCF_3;

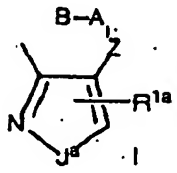
R is selected from H, F, Cl, Br, I, OR^3, SR^3, NO_2, and CH_2OR^3;

alternatively, E and R combine to form methylenedioxy or ethylenedioxy;

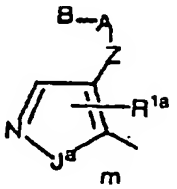
M is selected from the group:



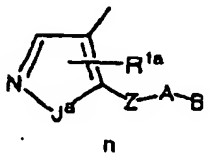
k



l



m



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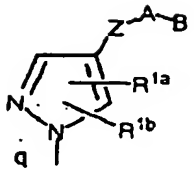
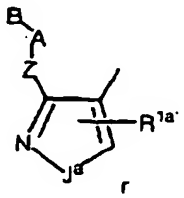
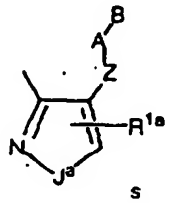


q



r



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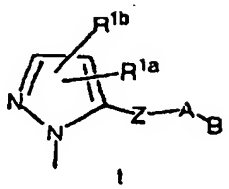
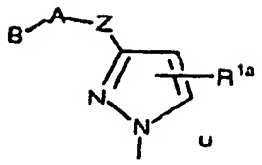


t



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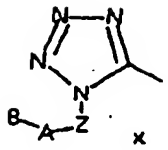
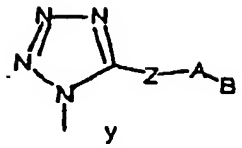


x

and



y

J^a is NH or NR^{1a};

Z is selected from C_{1-4} alkylene, $(CH_2)_rO(CH_2)_r$, $(CH_2)_rNR^3(CH_2)_r$, $-(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)O(CH_2)_r$, $(CH_2)_rOC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_rNR^3C(O)(CH_2)_r$, $(CH_2)_rOC(O)O(CH_2)_r$, $(CH_2)_rOC(O)NR^3(CH_2)_r$, $(CH_2)_rNR^3C(O)O(CH_2)_r$, $(CH_2)_rNR^3C(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, $(CH_2)_rSO_2NR^3(CH_2)_r$, $(CH_2)_rNR^3SO_2(CH_2)_r$, and $(CH_2)_rNR^3SO_2NR^3(CH_2)_r$, provided that Z does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with ring M or group A;

R^{1a} and R^{1b} are independently absent or selected from $-(CH_2)_r-R^{1'}$, $-CH=CH-R^{1'}$, $NCH_2R^{1"}$-, $OCH_2R^{1"}$, $SCH_2R^{1"}$, $NH(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$, and $S(CH_2)_2(CH_2)_tR^{1'}$;

alternatively, R^{1a} and R^{1b}, when attached to adjacent carbon atoms, together with the atoms to which they are attached form a 5-8 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^4 and which contains from 0-2 heteroatoms selected from the group consisting of N, O, and S;

alternatively, when Z is C(O)NH and R^{1a} is attached to a ring carbon adjacent to Z, then R^{1a} is a C(O) which replaces the amide hydrogen of Z to form a cyclic imide;

$R^{1'}$ is selected from H, C_{1-3} alkyl, F, Cl, Br, I, -CN, -CHO, $(CF_2)_rCF_3$, $(CH_2)_rOR^2$, NR^2R^{2a}, $C(O)R^{2c}$, $OC(O)R^2$, $(CF_2)_rCO_2R^{2c}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $CH(=NR^{2c})NR^2R^{2a}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^{2b}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^{2a}R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$, $NR^2SO_2R^{2b}$, C_{3-6} carbocyclic residue substituted with 0-2 R^4, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

$R^{1"}$ is selected from H, $CH(CH_2OR^2)_2$, $C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $S(O)R^{2b}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;

R^2, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2a}, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, phenethyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3b}, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3c}, at each occurrence, is selected from C_{1-4} alkyl, and phenyl;

A is selected from:

C_{3-10} carbocyclic residue substituted with 0-2 R^4, and
5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with C-2 R^4;

B is selected from: Y and X-Y;

X is selected from C_{1-4} alkylene, $-CR^2(CR^2R^{2b})(CH_2)_t-$, $-C(O)-$, $-C(=NR^{1'})-$, $-CR^2(NR^{1''}R^2)-$, $-CR^2(OR^2)-$, $-CR^2(SR^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-S(O)_p-$, $-S(O)_pCR^2R^{2a}-$, $-CR^2R^{2a}S(O)_p-$, $-S(O)_2NR^2-$, $-NR^2S(O)_2-$, $-NR^2S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S(O)_2NR^2-$, $-NR^2S(O)_2NR^2-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)O-$, $-OC(O)NR^2-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

Y is selected from:

$(CH_2)_rNR^2R^{2a}$, provided that X-Y do not form a N-N, O-N, or S-N bond,
C_{3-10} carbocyclic residue substituted with 0-2 R^{4a}, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$, $CH(=NS(O)_2R^5)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $C(O)NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2-C_{1-4}$ alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, $(CF_2)_rCF_3$, NCH_2R^{1*}, OCH_2R^{1*}, SCH_2R^{1*}, $N(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$, and $S(CH_2)_2(CH_2)_tR^{1'}$,

alternatively, one R^4 is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, $(CH_2)_r$-F, $(CH_2)_r$-Br, $(CH_2)_r$-Cl, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rNR^2R^{2b}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2-C_{1-4}$ alkyl, $C(O)NHSO_2-C_{1-4}$ alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, and $(CF_2)_rCF_3$;

alternatively, one R^{4a} is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-1 R^5;

R^{4b}, at each occurrence, is selected from H, =O, $(CH_2)_rCR^3$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $CH(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, $NR^3SO_2-C_{1-4}$ alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_pCF_3$, $S(O)_p-C_{1-4}$ alkyl, $S(O)_p$-phenyl, and $(CF_2)_rCF_3$;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

R^6, at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and

$NR^2SO_2C_{1-4}$ alkyl;

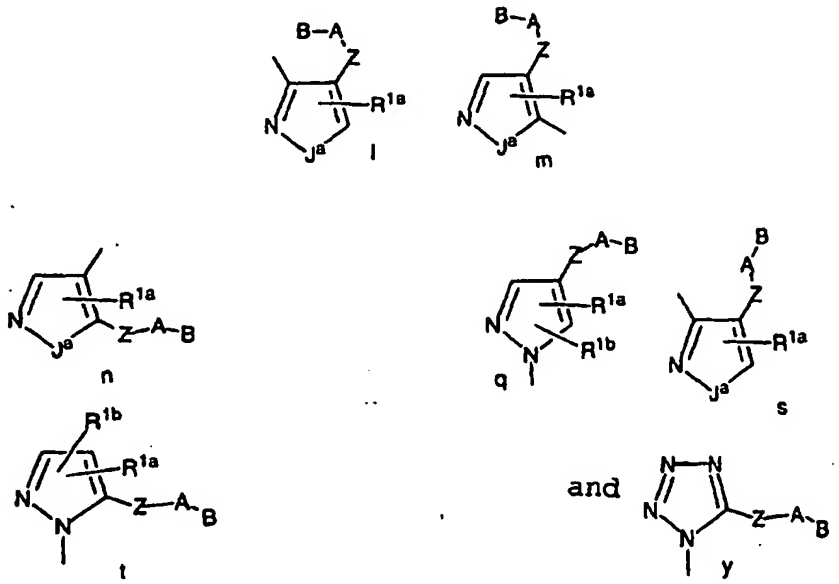
p is selected from 0, 1, and 2;

r is selected from 0, 1, 2, and 3;
and,

t is selected from 0 and 1.

[2] In a preferred embodiment, the present invention provides novel compounds, wherein M is selected from the group:

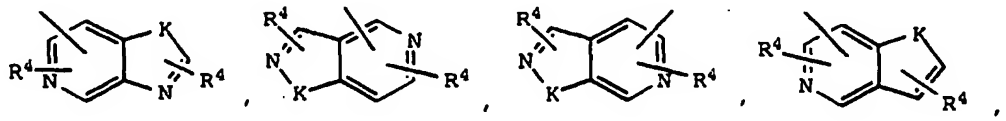
[0020]

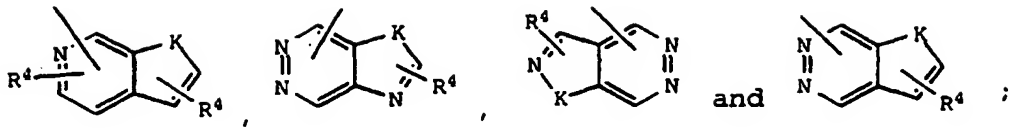


Z is selected from $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)O(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, and $(CH_2)_rSO_2NR^3(CH_2)_r$; and,

Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a}; phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, benzofuran, benzothiofuran, indole, benzimidazole, benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole, and isoindazole;

Y may also be selected from the following bicyclic heteroaryl ring systems:

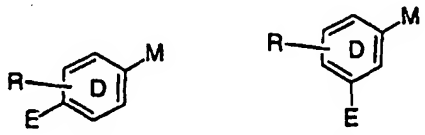




K is selected from O, S, NH, and N.

[3] In a more preferred embodiment, the present invention provides novel compounds of formula Ia or Ib:

[0021]



Ia Ib

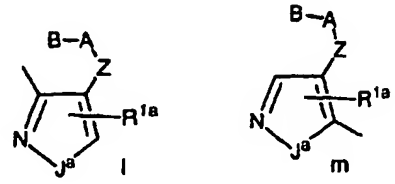
wherein;

ring D is phenyl or pyridyl:

E is selected from F, Cl, Br, and C_{1-3} alkoxy;

R is selected from H, F, Cl, Br, OR^3, and CH_2OR^3;

M is selected from the group:



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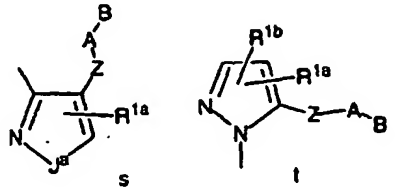

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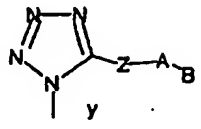


y

Z is selected from $(CH_2)_rC(O)(CH_2)_r$ and $(CH_2)_rC(O)NR^3(CH_2)_r$; and,

Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a}; phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,9-triazole, 1,2,5-triazole, 1,3,4-triazole, benzofuran, benzothiofuran, indole, benzimidazole, benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole, and isoindazole.

[4] In an even more preferred embodiment, the present invention provides novel compounds of formula Ia, wherein;

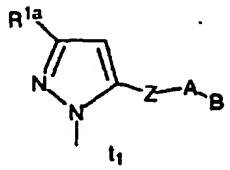
[0022]

ring D is phenyl;

E is selected from F, Cl, Br, and OCH_3;

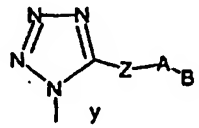
R is selected from H, F, Cl, and Br;

M is selected from the group:



t_1

and



A is selected from:

C_{5-6} carbocyclic residue substituted with 0-2 R^4, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a}; phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, benzimidazolyl, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, and 1,3,4-triazole;

R^2, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, C_{5-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2a}, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, phenethyl, C_{5-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{5-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{5-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a ring selected from imidazolyl, morpholino, piperazinyl, pyridyl, and pyrrolidinyl, substituted with 0-2 R^{4b};

R^4, at each occurrence, is selected from H, =O, OR^2, CH_2OR^2, F, Cl, C_{1-4} alkyl, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$, $CH(=NS(O)_2R^5)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $S(O)_2R^5$, and CF_3

provided that if B is H, then R^4 is other than tetrazole, C(O)-alkoxy, and $C(O)NR^2R^{2a}$;

R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, C_{1-4} alkyl, NR^2R^{2a}, $CH_2NR^2R^{2a}$, NR^2R^{2b}, $CH_2NR^2R^{2b}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_2R^5$, and CF_3; and,

R^{4b}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$, F, Cl, C_{1-4} alkyl, NR^3R^{3a}, $CH_2NR^3R^{3a}$, $C(O)R^3$, $CH_2C(O)R^3$, $C(O)OR^{3c}$, $C(O)NR^3R^{3a}$, $CH(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_2CF_3$, $S(O)_2$-C_{1-4} alkyl, $S(O)_2$-phenyl, and CF_3.

[5] In a further even more preferred embodiment, the present invention provides novel compounds selected from:

[0023]

3-Methyl-1-(2-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(3-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(2-hydroxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(3-hydroxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-hydroxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-bromo-4-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-iodo-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-methyl-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-carboxyldimethylamine)phenyl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-pyrrolidinocarbonyl)phenyl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-a-methyl-N-pyrrolidino)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-pyrrolidinocarbonyl)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-methanesulfonyl)phenyl)pyridin-2-yl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-N-pyrrolidinocarbonyl)pyridin-2-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-N-pyrrolidinocarbonyl)pyridin-2-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-sulfonamido)phenyl)pyridin-2-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-3-hydroxypyrrolidino)phenyl)carboxyamide;

1-(4-Methoxyphenyl)-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]tetrazole;

3-Methyl-1-(4-methoxy-3-chloro)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-trifluoromethoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(3-Bromophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(3-Iodophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(3,4-Methylenedioxanephenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4-Methoxyphenyl)-3-hydroxylmethylene-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide;

1-(4-Methoxyphenyl)-3-formaldehyde-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide;

1-(4-Methoxyphenyl)-5-(4'-pyrrolidinocarbonyl)anilide-3-pyrazolecarboxylic acid;

1-(4-Methoxyphenyl)-3-methylcarboxylate-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide;

1-(4'-Chlorophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Chlorophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1-pyridyl-1'-phenyl]-4-yl)carboxyamide;

1-(3',4'-Dichlorophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(3'-Chlorophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(9-methoxyphenyl)-3-(methylthio)pyrazole-5-carboxamide;

1-(4-Methoxyphenyl)-3-(methylsulfonyl)-N-(5-(2'-methylsulfonylphenyl)pyrimid-2-yl)pyrazole-5-carboxamide;

N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazole-5-carboxamide;

N-(4-Benzoylpyrrolidino)-1-(4-methoxyphenyl)-3-(methylthio)-1H-pyrazole-5-carboxamide;

1-(4-Methoxyphenyl)-N-(5-(2'-methylsulfonylphenyl)pyrimid-2-yl)-3-(methylthio)-1H-pyrazole-5-carboxamide;

N-(4-Benzoylpyrrolidino)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazole-5-carboxamide;

N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methoxymethyl)-1H-pyrazole-5-carboxamide;

N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-carbomethoxy-1H-pyrazole-5-carboxamide;

N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylsulfonylmethyl)-1H-pyrazole-5-carboxamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-methanesulfonyl)phenyl)pyrimidin-2-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-2-carbomethoxypyrrolidino)phenyl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-3-aminopyrrolidino)phenyl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-3-methoxypyrrolidino)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-aminosulfonyl)phenyl)pyridin-2-yl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-amidino)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-pyrrolidino)formylimino)phenyl)carboxyamide;

3-Trifluoromethyl-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))-1-(4-methoxyphenyl)pyrrolo[3,4-d]pyrazole-4,6-(1H, 5H)-dione;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-carbomethoxy-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)) carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-hydoxymethyl-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-2-fluoro(4-(N-pyrrolidino)formylimino)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-pyrrolidino)formyl-N-((2-propyl)methylcarbamoyl) imino)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-pyrrolidino)formyl-N-(methanesulfamoyl)imino) phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((4-amidino)phenyl)methyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((4-(N-pyrrolidino)formylimino)phenyl)methyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((1-benzyl)piperidin-4-yl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((1-(pyridin-2-yl)methyl)piperidin-4-yl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(2-methylimidazo-1-yl))phenyl)carboxyamide;

3-Methyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-(4-(5-methylimidazol-1-yl}phenyl)carboxyamide;

3-Methyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-(4-(4-methylimidazol-1-yl}phenyl)carboxyamide,;

3-Trifluoromethyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(5-carbomethoxy-imidazol-1-yl}phenyl)carboxyamide;

3-Trifluoromethyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(5-carboxy-imidazol-1-yl}phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-3-hydroxylmethyl-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-3-formaldehyde-1H-pyrazole-5-N-(4'-(pyrrolidinocarbonyl)phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-5-N-(4'-(pyrrolidinocarbonyl)anilide)-1H-pyrazol-3-yl-carboxylic acid;

1-(4'-Methoxyphenyl)-3-methylcarboxylate-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-3-cyanomethyl-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phenyl)carboxyamide;

2-(1'-(4"-Methoxyphenyl)-5'-(4"-pyrrolidinyl-one)anilide-1H-pyrazol-3'-yl)acetic acid;

1-(4'-Methoxyphenyl)-3-bromomethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Methoxyphenyl)-3-aminomethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Methoxyphenyl)-3-(N-methylsulfonylamino)methyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide;

1-(4'-Methoxyphenyl)-3-(imidazol-1-yl)methyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Methoxyphenyl)-3-hydroacylmethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Methoxyphenyl)-3-trifluoroacetylhydroxylmethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-methylsulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Methoxy-2'-hydroxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-methylsulfonyl-[1,1']-biphen-4-yl) carboxyamide;

1-(4'-Methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide;

1-(4'-Methoxy-2'-hydroxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-tert-butylaminosulfonyl-[1,1']-biphenyl)carboxyamide;

1-(4'-Methoxy-2'-hydroxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide;

1-(4'-Methoxy-2'-hydroxylmethylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide;

1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-sec-butyl)phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-(3"-methyl-3"-pyrazolin-5"-one-2"-yl)phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-(6"-methylbenzothiazol-2"-yl)phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(3',4'-dibromophenyl)carboxyamide;

1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-n-butyl)phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-(4"-methylpiperidino)phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-(2"-methylimidazol-1"-yl)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-carboxy(N-methylimidazo-2-yl)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-hydroxymethyl(2-(imidazol-2-yl)phenyl)))carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-hydroxymethyl(2-(1-benzyl-imidazol-2-yl)phenyl)))

carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-(N-(4-(2-carboxy(imidazol-2-yl)phenyl)))carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-(4-methoxyphenyl)amino-(2-thiazolyl)methyl) phenyl)))carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-(N-(4-(2-carboxy-(4,5-dihyrothiazol-2-yl)phenyl)))carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-4-(2-(4',5'-dihydro-1'H-imidazol-2'yl)phenyl)carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(4-(N-2'-aminoethylenecarboxyamide)phenyl)carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-[4-(1,4,5,6-tetrahydro-pyrimid-2-yl)-phenyl)carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-[4-(N-methyl-4,5,6-trihydro-pyrimid-2-yl)-phenyl)carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-1-(2-fluoro-4-imidazolinephenyl)carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-1-(2-fluoro-4-N-methylimidazolinephenyl)carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-[4-(4,5-dihydro-1-N-methyl-imidazo-2-yl)phenyl)carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-[4-carbonylguanidine)phenyl]carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-[4-(pyrimidin-2-yl)phenyl]carboxyamide;

1-[(4-Methoxy)phenyl]-3-(ethoxycarbonyl)-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-(carboxyamide)-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(2-hydroxyethyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-[(4-Methoxy)phenyl)-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide-3-hydroxamic acid;

1-[(4-Methoxy)phenyl]-3-[phenylcarboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(3-hydroxypropyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[methylcarboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(benzyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(dimethyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboacyamide;

1-[(4-Methoxy)phenyl]-3-[(phenylethyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(2-hydroxyphenyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)car-

boxyamide;

1-[(4-Methoxy)phenyl]-3-[(3-hydroxyphenyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(4-hydroxyphenyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(methoxycarbonyl)amino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-amino-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(methoxycarbonyl)methylamino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(2-hydroxy)ethylamino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[E-2-(methoxycarbonyl)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[2-(methoxycarbonyl)ethyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[E-2-(carboxy)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[2-(carboxy)ethyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[E-2-(carboxyamide)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[E-2-(hydroxymethyl)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-(3-hydroxypropyl)-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-propyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-cyano-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl) carboxyamide;

1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-(amidino)-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-(N-hydroxyamidino)-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-(ethoxycarbonyl)-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide; and,

1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide-4-carboxylic acid;

and pharmaceutically acceptable salts thereof.

DEFINITIONS

[0024] The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

[0025] The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties.

[0026] The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

[0027] When any variable (e.g., R^6) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6, then said group may optionally be substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of R^6. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0028] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0029] As used herein, "C_{1-6} alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, examples of which include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl; "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like.

[0030] "Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like.

[0031] As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl,; [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2] bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

[0032] As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from tne group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heterotams independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

[0033] Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*, 6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl,

isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1*H*-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

[0034] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0035] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

[0036] The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

[0037] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

SYNTHESIS

[0038] The compounds of Formula I can be prepared using the reactions and techniques described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (Protective *Groups In Organic Synthesis,* Wiley and Sons, **1991**).

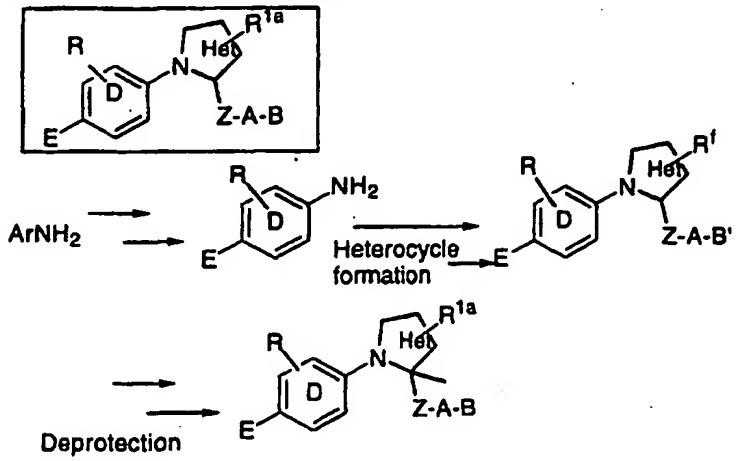
Preparation of compounds of FORMULA I with a five-membered heterocyclic core

[0039] General syntheses for compounds of Formula I are outlined in Schemes 1a-b. The M ring may be N-linked or C-linked to the ring referred to in the following scheme as ring D. B' and R^f are protected functional groups that can be converted to R, B and R^{1a} respectively. It is understood that group E may or may not be protected or a precursor to E of Formula I, depending upon the demands of the chemistry involved. The compounds can also be obtained by changing the sequences of the reaction steps as described in Scheme 1. For N-linked M ring, the appropriate amine-substituted ring D is treated under conditions described in "The Chemistry of Heterocyclic Compounds, Weissberger, A. and Taylor, E. C. Ed.,John Wiley & Sons" or as described later in the synthesis section to give N-linked ring M.

Further modifications and deprotections give N-linked ring M with R, Z-A-B and R^{1a} substitutents.

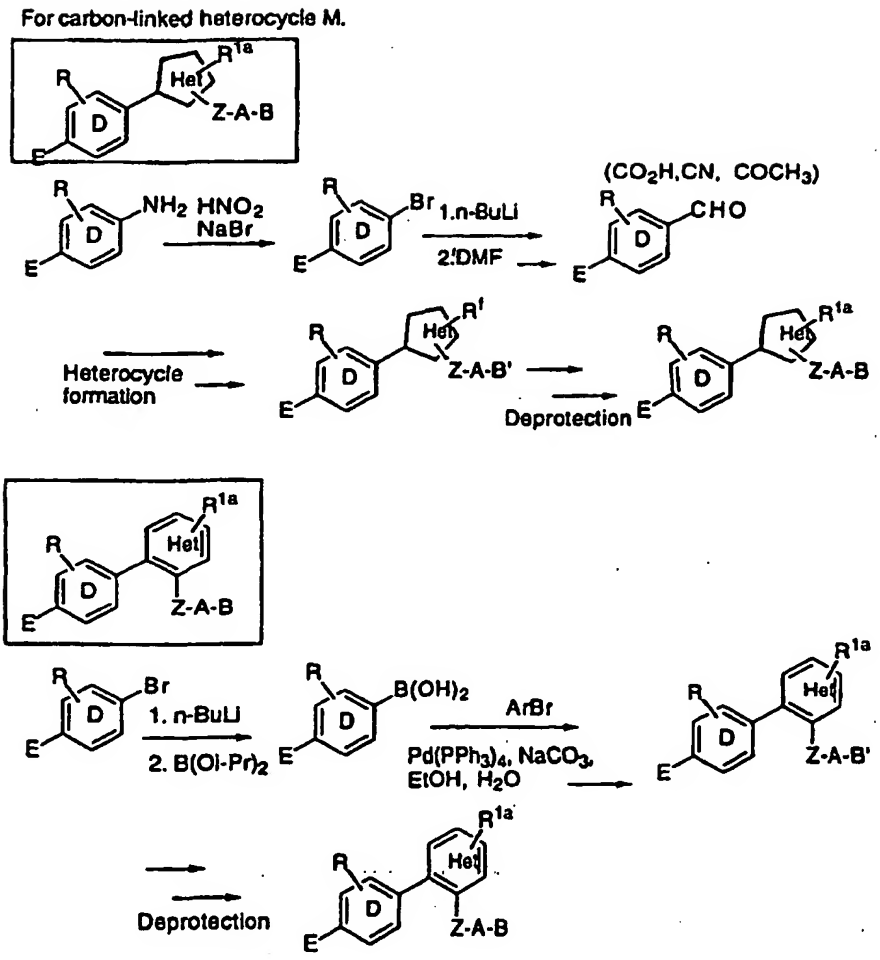
Scheme 1a

For Nitrogen-linked heterocycle M.



[0040] For C-linked five-membered ring M, the above aniline is diazotized with nitrous acid and treated with NaBr to give the heterocyclic bromide. Treatment with n-BuLi followed by DMF gives aldehyde which can be converted to ring M as described in "The Chemistry of Heterocyclic Compounds, Weissberger, A. and Taylor, E. C. Ed., John Wiley & Sons" or as described later in the synthesis section. Other precursor functional groups like acid, cyanide, methylketone, etc. can also be used to form the ring M. Further modifications and deprotections can yield five-membered ring M substituted with R, Z-A-B and R^{1a}. The corresponding C-linked six-membered ring M can be obtained by converting the above bromide with n-butyl lithium and triisopropyl borate to give the heterocylic boronic acid. Suzuki coupling with the appropriate heterocyclic bromide, followed by modifications and deprotections gives the C-linked six-membered ring M with R, Z-A-B and R^{1a} substitutents.

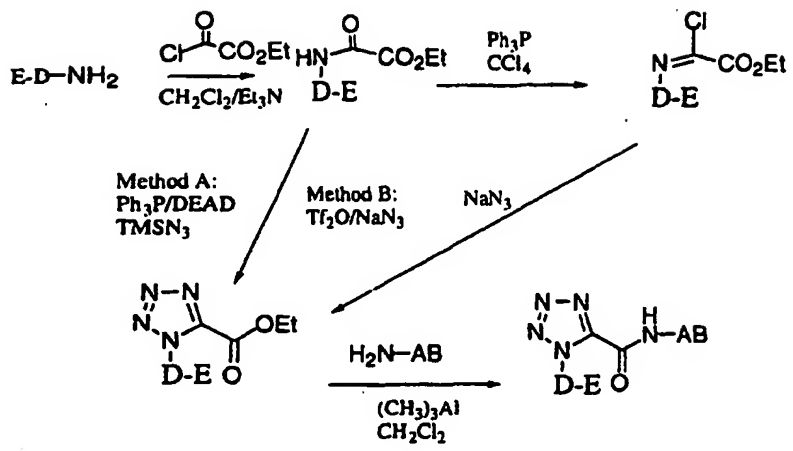
SCHEME 1b



[0041] The tetrazole compounds of this invention where Z is-CONH-can be prepared as exemplified in Scheme 3. An appropiately substituted amine (E-D-NH_2) is acylated with ethyl oxalyl chloride. The resulting amide can be converted to the tetrazole either by the methods described by Duncia (*J. Org. Chem.* **1991,** 2395-2400) or Thomas (*Synthesis* **1993,** 767-768, 1993). The amide can be converted to the iminoyl chloride first and the reacted with NaN_3 to form the 5-carboethoxytetrazole (*J. Org. Chem.* **1993,** *58,* 32-35 and *Bioorg. & Med. Chem. Lett.* **1996,** *6,* 1015-1020). The 5-carboethoxytetrazole is then coupled with an appropriate amine ($HANH_2$) by the method described by Weinreb (*Tetr. Lett.* **1977,** *48,* 4171-4174). Final deprotection as described before yields the desire product.

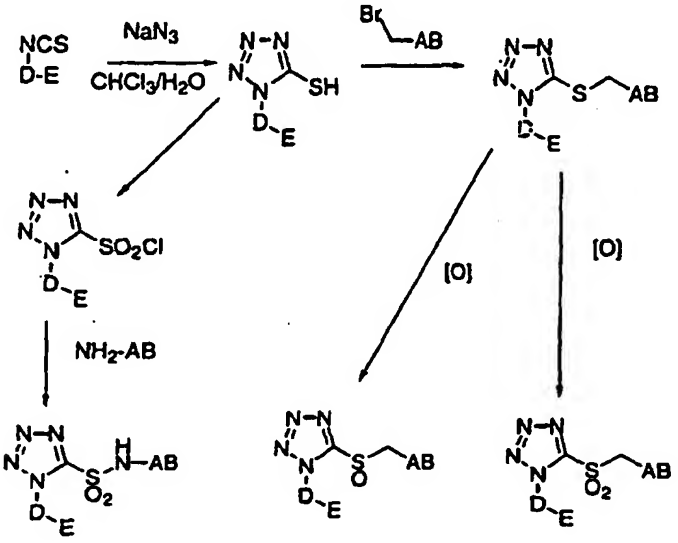
[0042] The tetrazole compounds of this invention where Z is-CO- can also be prepared via iminoyl chloride (*Chem. Ber.* **1961,** *94,* 1116 and *J. Org. Chem.* **1976,** *41,* 1073) using an appropriately substituted acyl chloride as starting material. The ketone-linker can be reduced to compounds where Z is alkyl.

Scheme 3



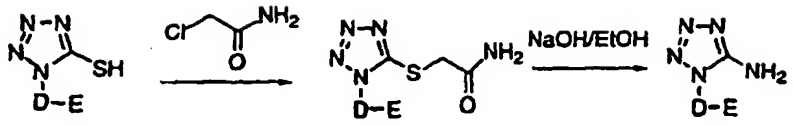
[0043] The tetrazole compounds of this invention where Z is-SO_2NH-, -S-, -S(O), SO_2-can be prepared as exemplified in Scheme 4. Appropiately substituted thioisocyanate is reacted with sodium azide to give the 5-thiotetrazole (*J. Org. Chem.* **1967**, *32*, 3580-3592). The thio-compound can be alkylated (*J. Org. Chem.* **1978**, *43*, 1197-1200) and then oxydized to the sulfoxide or sulfone. The thio-compound can also be converted to the sulfonyl chloride and the reacted with an amine to give the desired sulfonamide. The tetrazole compounds of this invention where Z is-O-can be prepared via the same method described in Scheme 4 by using appropiately substituted isocyanate as the startimg material.

Scheme 4



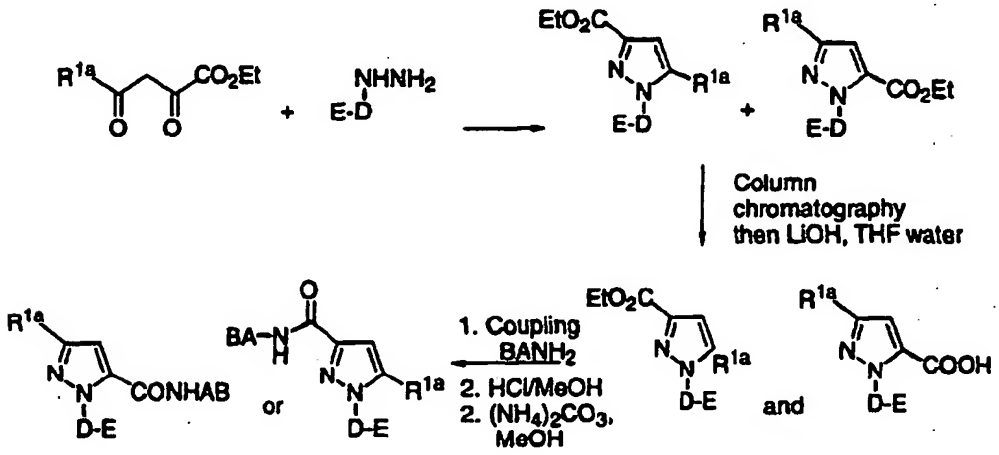
[0044] The tetrazole compounds of this invention where Z is-NH-, -NHCO-, -$NHSO_2$-can be prepared from 5-aminotetrazole, which can be prepared by Smiles Rearrangement as shown in Scheme 5. The thio-compound prepared as described in Scheme 4 is alkylated with 2-chloroacetamide. The resulting compound is then refluxed in ethanolic sodium hydroxide to give the corresponding 5-amino-tetrazole (*Chem. Pharm. Bull.* **1991**, *39*, 3331-3334). The resulting 5-amino-tetrazole can then be alkylated or acylated to form the desired products.

Scheme 5



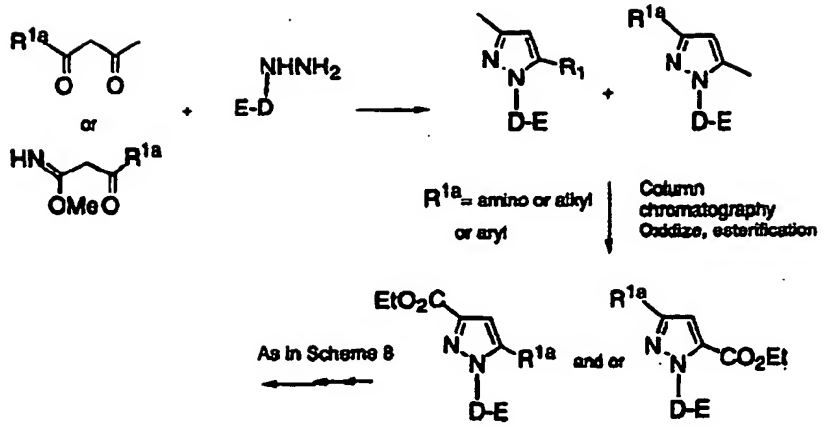
[0045] As shown in Scheme 8, pyrazole ring M of the general Formula I such as those described in Scheme 1 can be prepared by the condensation of an appropriately substituted hydrazine with a variety of diketo esters. Condensations of this type typically afford a mixture of pyrazole regioisomers which can be effectively separated via silica gel column chromatography. Hydrolysis of the esters followed by coupling with an appropriate amine can afford the desired amide intermediate. Various substituents on the pyrazole N1 can then be manipulated to afford a variety of benzo, heterocyclic and bicylic compounds

Scheme 8



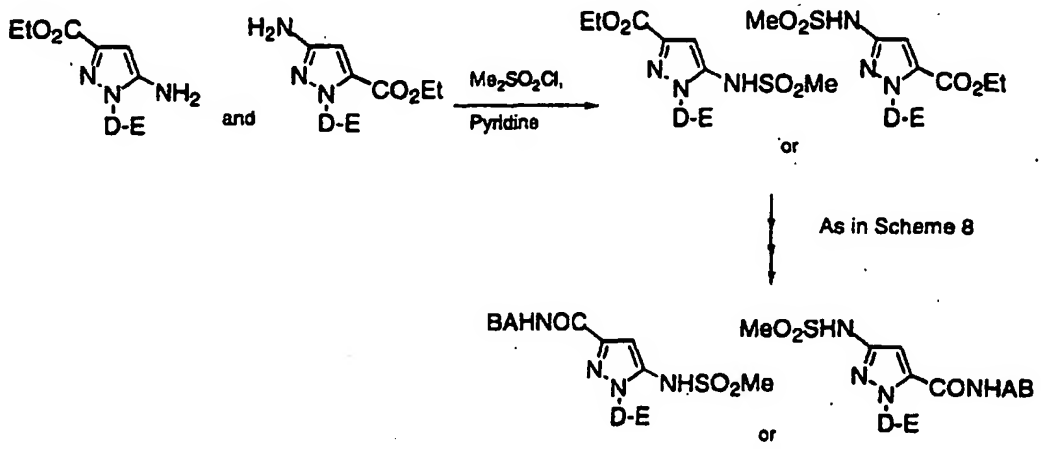
[0046] The above methodology when applied to diketo derivatives also affords a mixture of pyrazole regioisomers. These can be further manipulated to afford the compounds of Formula I as shown in Scheme 9.

Scheme 9



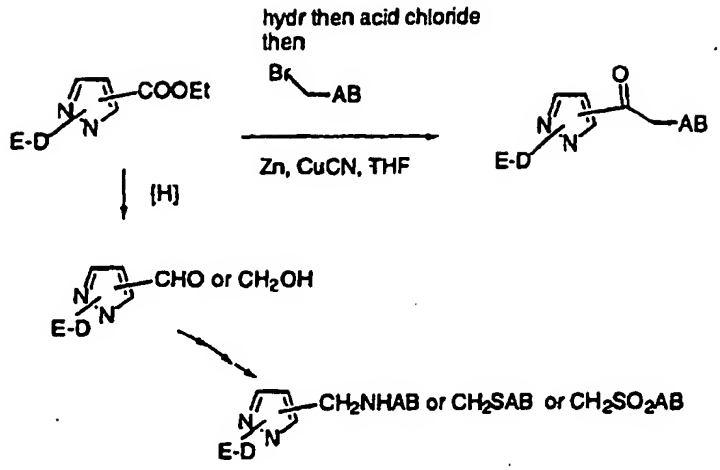
[0047] When ketoimidates are used for condensations with hydrazines the corresponding pyrazole amino esters regioadducts are obtained (Scheme 9). Conversion of these intermediates to the final compounds of formula I can then be accomplished by the protection of the amino functionality with a suitable protecting group commonly known to those in the art or by derivatization (such as a sulfonamide as in Scheme 10) then following the general synthetic strategy to prepare the compounds of this invention.

Scheme 10



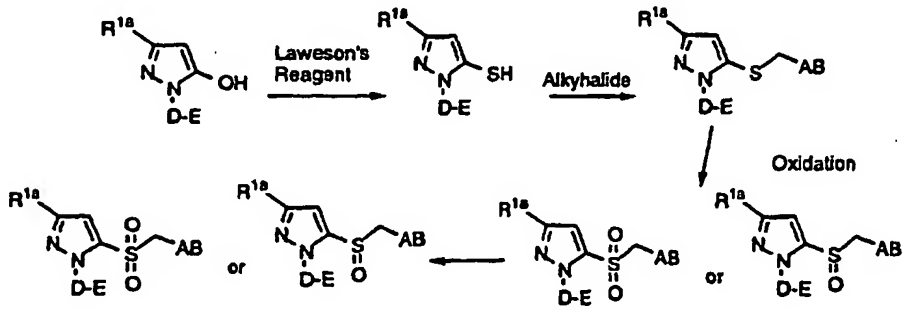
[0048] The pyrazole ester intermediate can be further manipulated to the ketones by the cuprate methodology described by Knochel et. al (Scheme 11). Alternatively the ester can be reduced to either the alcohol or aldehyde via methods known to those in the art followed by either a reductive amination with an appropriate amine to an alkyl amine or by converting the alcohol to a leaving group which in turn can be displaced with a number of nucleophiles to provide the intermediates which on further manipulations should afford the compounds of this invention.

Scheme 11



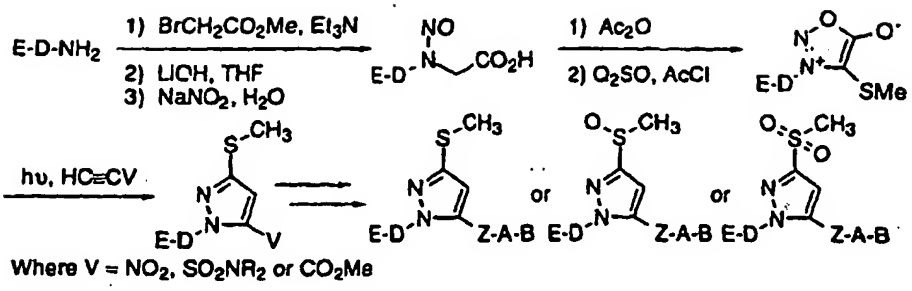
[0049] Thio compounds such as those described in Scheme 12 can be easily prepared by the conversion of 5-hydroxy pyrazole to its thiol by treatment with Lawesson's reagent in refluxing toluene.

Scheme 12



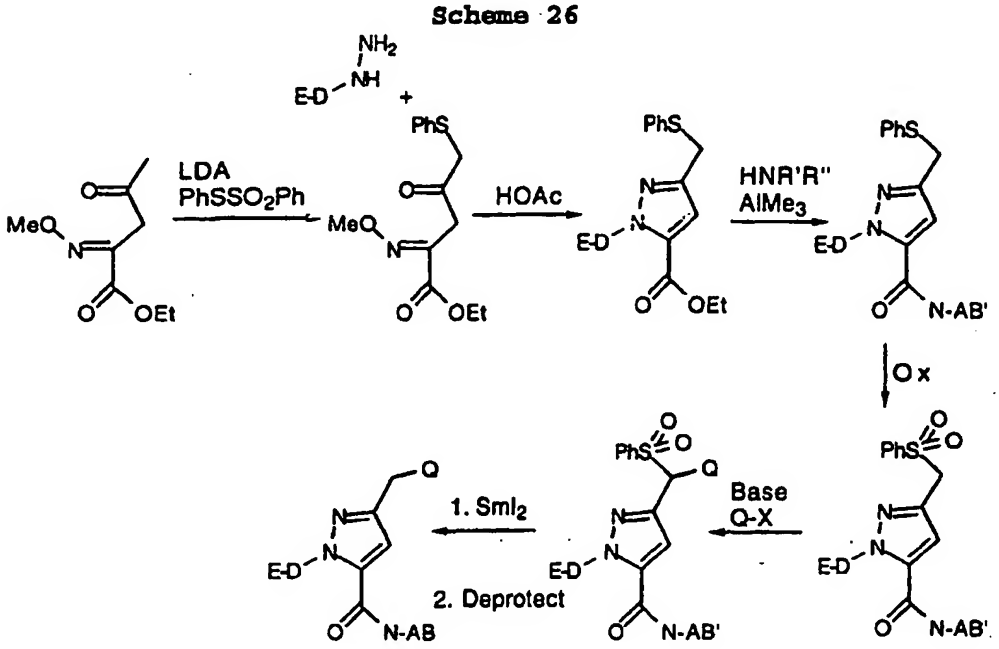
[0050] Scheme 23 describes the general synthesis for pyrazoles which have thio and oxidized sulfur derivatives. An appropriately substituted amine is alkylated with ethyl bromoacetate and hydrolyzed to the glycine derivative. Preparation of the N-nitroso compound was easily achieved with sodium nitrite (*J. Chem. Soc.* **1935,** 899). Cyclization to the syndone using acetic anhydride (*J. Chem. Soc.* **1935,** 899) was following by the introduction of the sulfide unit using a sulfoxide as solvent and acetyl chloride as a activating reagent (*Tetr.* **1974**, *30*, 409). Photolytic cleavage of the sydnone in the presence of an acetylenic compound the 1,3,5 trisubstituted pyrazole as the major regioisomer (*Chem. Ber.* **1979**, *112*, 1206). These can be carried on, as described before, to the final compounds containing the sulfide, sulfoxide or sulfone functionality.

Scheme 23



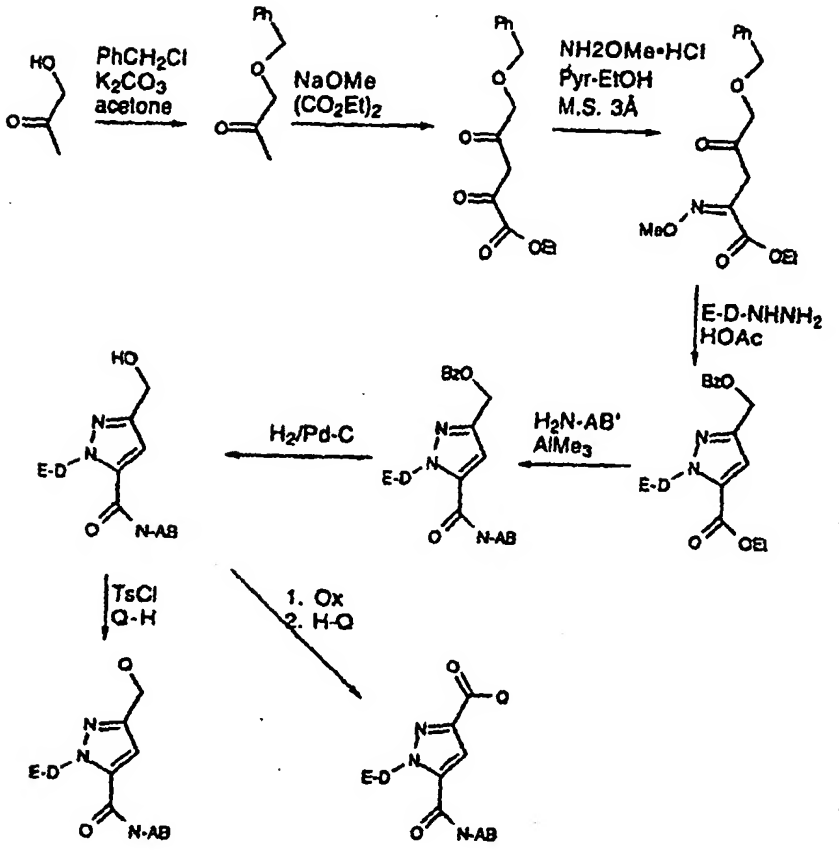
[0051] When core substitutent R^{1a} is CH_2Q, the synthesis is shown in Scheme 26. After being treated with LDA, the ketone starting material reacts with $PhSSO_2Ph$ to give the phenylthiolated compound which reacts with hydrazine in acetic acid to form pyrazole derivative. The pyrazole ester reacts with an amine or aniline (previously treated with $AlMe_3$) to provide amide. Oxidation of the sulfide with mCPBA gives the corresponding sulfone. Deprotonation of the sulfone with base, followed by trapping with an electrophile (Q-X) and treatment with SmI_2 provided the desired compound after deprotection.

Scheme 26



[0052] Scheme 27 shows other methods of synthesis for $R^{1a} = CH_2Q$ or COQ. Protection of the hydroxyl group of hydroxyacetone with a benzyl halide and treatment with a base and $CO(CO_2Et)_2$ gives the tricarbonyl compound. Refluxing with $NH_2OMe{\cdot}HCl$ in pyridine and ethanol in the presence of molecular sieve 3Å gives the oxime. Cyclization of oxime with E-D-$NHNH_2$ provided pyrazole, which can be converted into the corresponding amide by reacting with an amine or aniline (previously activated with $AlMe_3$). Debenzylation by catalytic hydrogenation provides the alcohol. The alcohol is converted into the tosylate with TsCl, followed by replacement with a nucleophile to provide the desired compound. The alcohol can also be oxidized to the corresponding aldehyde or acid, or further converted to ester or amide.

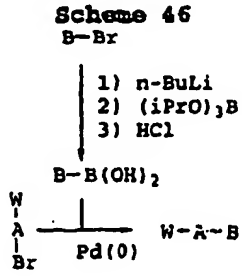
Scheme 27



Preparation of group A-B of FORMULA I

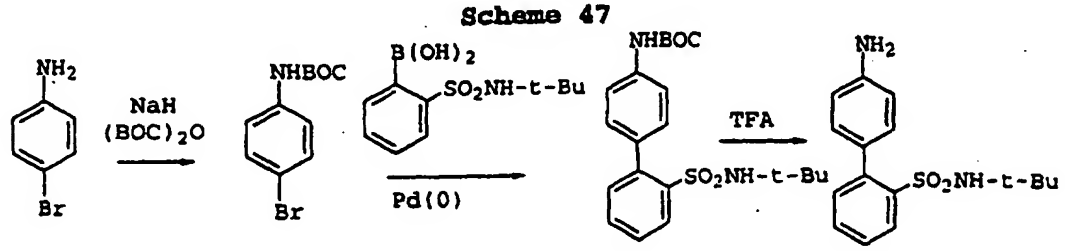
[0053] Compounds of this invention where B is either a carbocyclic or heterocyclic residue as defined in Formula 1 are coupled to A as shown generically and by specific example in Schemea 46 and 47, respectively. Either or both of A and B may be substituted with 0-2 R^4. W is defined as a suitable protected nitrogen, such as NO_2 or NHBOC; a protected sulfur, such as S-tBu or SMOM; or a methyl ester. Halogen-metal exchange of the bromine in bromo-B with n-butyl lithium, quenching with triisopropyl borate and acidic hydrolysis gives the required boronic acid, B-$B(OH)_2$. The W-A-Br subunit may be already linked to ring M before the Suzuki coupling reaction. Deprotection provides the complete subunit.

Scheme 46



[0054] Scheme 47 describes a typical example of how the A-B subunit is prepared for attachment to ring M. 4-Bromoaniline is protected as Boc-derivative and the coupled to 2-(t-butylamino)sulfonylphenylboronic acid under Suzuki conditions. 2-(t-Butylamino)sulfonylphenylboronic acid is prepared by the method described by Rivero (*Bioorg. Med. Chem. Lett.* **1994**, 189). Deprotection with TFA can provide the aminobiphen-4-yl compound. The aminobiphen-4-yl is then coupled to the core ring structures as described below.

Scheme 47



[0055] When B is defined as X-Y, the following description applies. Groups A and B are available either through commercial sources, known in the literature or readily synthesized by the adaptation of standard procedures known to practitioners skilled in the art of organic synthesis. the required reactive functional groups appended to analogs of A and B are also available either through commercial sources, known in the literature or readily synthesized by the adaptation of standard procedures known to practitioners skilled in the art of synthesis. In the tables that follow the chemistry required to effect the coupling of A to B is outlined.

Table A:

Preparation of Amide Ester, Urea, Sulfonamide andSulfamide Linkages Between A and B.		
If A contains:	then the reactive substituent of Y is:	to give the following product A-X-Y:
A-NHR^2 as a substituent	ClC(O)-Y	A-NR^2-C(O)-Y
a secondary NH as part of a ring or chain	ClC(O)-Y	A-C(O)-Y
A-OH as a substituent	ClC(O)-Y	A-O-C(O)-Y
A-NHR^2 as a substituent	ClC(O)-CR^{2}R^{2a}-Y	A-NR^2-C(O)-CR^{2}R^{2a}-Y
a secondary NH as part of a ring or chain	ClC(O)-CR^{2}R^{2a}-Y	A-C(O)-CR^{2}R^{2a}-Y
A-OH as a substituent	ClC(O)-CR^{2}R^{2a}-Y	A-O-C(O)-CR^{2}R^{2a}-Y
A-NHR^2 as a substituent	ClC(O)-CNR^2-Y	A-NR^2-C(O)-CNR^2-Y
a secondary NH as part of a ring or chain	ClC(O)-CNR^2-Y	A-C(O)-CNR^2-Y
A-OH as a substituent	ClC(O)-CNR^2-Y	A-O-C(O)-CNR^2-Y
A-NHR^2 as a substituent	ClSO$_2$-Y	A-NR^2-SO$_2$-Y
a secondary NH as part of a ring or chain	ClSO$_2$-Y	A-SO$_2$-Y
A-NHR^2 as a substituent	ClSO$_2$-CR^{2}R^{2a}-Y	A-NR^2-SO$_2$-CR^{2}R^{2a}-Y
a secondary NH as part of a ring or chain	ClSO$_2$-CR^{2}R^{2a}-Y	A-SO$_2$-CR^{2}R^{2a}-Y
A-NHR^2 as a substituent	ClSO$_2$-NR^2-Y	A-NR^2-SO$_2$-NR^2-Y
a secondary NH as part of a ring or chain	ClSO$_2$-NR^2-Y	A-SO$_2$-NR^2-Y

Table A: (continued)

Preparation of Amide Ester, Urea, Sulfonamide andSulfamide Linkages Between A and B.		
If A contains:	then the reactive substituent of Y is:	to give the following product A-X-Y:
A-C(O)Cl	HO-Y as a substituent	A-C(O)-O-Y
A-C(O)Cl	NHR^2-Y as a substituent	A-C(O)-NR^2-Y
A-C(O)Cl	a secondary NH as part of a ring or chain	A-C(O)-Y
A-CR^2R^{2a}C(O)Cl	HO-Y as a substituent	A-CR^2R^{2a}C(O)-O-Y
A-CR^2R^{2a}C(O)Cl	NHR^2-Y as a substituent	A-CR^2R^{2a}C(O)-NR^2-Y
A-CR^2R^{2a}C(O)Cl	a secondary NH as part of a ring or chain	A-CR^2R^{2a}C(O)-Y
A-SO_2Cl	NHR^2-Y as a substituent	A-SO_2-NR^2-Y
A-SO_2Cl	a secondary NH as part of a ring or chain	A-SO_2-Y
A-$CR^2R^{2a}SO_2$Cl	NHR^2-Y as a substituent	A-$CR^2R^{2a}SO_2$-NR^2-Y
A-$CR^2R^{2a}SO_2$Cl	a secondary NH as part of a ring or chain	A-$CR^2R^{2a}SO_2$-Y

[0056] The chemistry of Table A can be carried out in aprotic solvents such as a chlorocarbon, pyridine, benzene or toluene, at temperatures ranging from-20°C to the reflux point of the solvent and with or without a trialkylamine base.

Table B:

Preparation of Ketone Linkages between A and B.		
If A contains:	then the reactive substituent of Y is:	to give the following product A-X-Y:
A-C(O)Cl	BrMg-Y	A-C(O)-Y
A-CR^2R^{2a}C(O)Cl	BrMg-Y	A-CR^2R^{2a}C(O)-Y
A-C(O)Cl	BrMgCR^2R^{2a}-Y	A-C(O)CR^2R^{2a}-Y
A-CR^2R^{2a}C(O)Cl	BrMgCR^2R^{2a}-Y	A-CR^2R^{2a}C(O)CR^2R^{2a}-Y

[0057] The coupling chemistry of table B can be carried out by a variety of methods. The Grignard reagent required for Y is prepared from a halogen analog of Y in dry ether, dimethoxyethane or tetrahydrofuran at 0°C to the reflux point of the solvent. This Grignard reagent can reacted directly under very controlled conditions, that is low temperature (-20°C or lower) and with a large excess of acid chloride or with catalytic or stoichiometric copper bromide·dimethyl sulfide complex in dimethyl sulfide as a solvent or with a variant thereof. Other methods available include transforming the Grignard reagent to the cadmium reagent and coupling according to the procedure of Carson and Prout (Org. Syn. Col. Vol. 3 601, 1955) or coupling mediated by $Fe(acac)_3$ according to Fiandanesse et al. (Tet. Lett., 4805, 1984), or a coupling mediated by manganese(II) catalysis (Cahiez and Laboue, Tet. Lett., 33(31), 4437, 1992).

Table C:

Preparation of Ether and Thioether linkages betweenA and B.		
If A contains:	then the reactive substituent of Y is:	to give the following product A-X-Y:
A-OH	Br-Y	A-O-Y
A-CR^2R^{2a}-OH	Br-Y	A-CR^2R^{2a}O-Y
A-OH	Br-CR^2R^{2a}-Y	A-OCR^2R^{2a}-Y
A-SH	Br-Y	A-S-Y
A-CR^2R^{2a}-SH	Br-Y	A-CR^2R^{2a}S-Y

Table C: (continued)

Preparation of Ether and Thioether linkages betweenA and B.		
If A contains:	then the reactive substituent of Y is:	to give the following product A-X-Y:
A-SH	Br-CR^2R^{2a}-Y	A-SCR^2R^{2a}-Y

[0058] The ether and thioether linkages of Table C can be prepared by reacting the two components in a polar aprotic solvent such as acetone, dimethylformamide or dimethylsulfoxide in the presence of a base such as potassium carbonate, sodium hydride or potassium t-butoxide at a temperature ranging from ambient to the reflux point of the solvent used.

Table D:

Preparation of -SO-and-SO_2-linkages from thioether of Table C.		
If the starting material is:	then it is oxidized with wet Alumina/Oxone to give:	then it is oxidized with m-chloroperbenzoic acid to give:
A-S-Y	A-S(O)-Y	A-SO_2-Y
A-CR^2R^{2a}S-Y	A-CR^2R^{2a}S(O)-Y	A-$CR^2R^{2a}SO_2$-Y
A-SCR^2R^{2a}-Y	A-S(O)CR^2R^{2a}-Y	A-$SO_2CR^2R^{2a}$-Y

[0059] The thioethers of Table C serve as a convenient starting material for the preparation of the sulfoxide and sulfone analogs of Table D. A combination of wet alumina and Oxone can provide a reliable reagents for the oxidation of the thioether to the sulfoxide as shown by Greenhalgh (Syn. Lett., 235, 1992). The sulfone can be prepared according to the method of Satoh (Chem. Lett., 381, 1992) using m-chloroperbenzoic acid.

[0060] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration fo the invention and are not intended to be limiting thereof.

EXAMPLES

[0061] Abbreviations used in the Examples are defined as follows: "°C" for degrees Celsius, "d" for doublet, "dd" for doublet of doublets, "eq" for equivalent or equivalents, "ESMS" for electrospray mass spectroscopy, "H" for hydrogen or hydrogens, "h" for hour or hours, "g" for gram or grams, "m" for multiplet, "M" for molar, "mg" for milligram or milligrams, "MHz" for megahertz, "min" for minute or minutes, "mL" for milliliter or milliliters, "MS" for mass spectroscopy, "nmr" or "NMR" for nuclear magnetic resonance spectroscopy, "t" for triplet, "TLC" for thin layer chromatography, "BOP" for benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, "DMAP" for dimethylaminopyridine, "DME" for dimethoxyethane, "EDAC" for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, "LAH" for lithium aluminium hydride, "NBS" for N-bromosuccinimide, "PyBrop" for bromo-tris-pyrrolidinophosphonium hexafluorophosphate, "TBAF" for tetrabutylammonium fluoride, "TBS-Cl" for t-butyldimethylsilyl chloride, and "TEA" for triethylamine.

REFERENCE EXAMPLE 1

3-Methyl-1-phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxyamide

[0062] **Ethyl 2-N-(methoxy)imino-4-oxopentanoate:** A mixture of ethyl pentanoate-2,4-dione (24.5 g, 154.9 mmol) and methoxyamine hydrogen chloride (13.58 g, 162.6 mmol) in ethanol (100 mL) was allowed to stand over activated 3 A molecular sieves (75 g) at ambient temperature for 18h. Following removal of the molecular sieves by filtration, dichloromethane (100 mL) was added and the reaction filtered. The resulting solution was evaporated and the residue applied to a silica gel column. The title compound was isolated in a homogenous form by elution with 5:1 hexane:ethyl acetate to give 9.09 g of product.

[0063] **Ethyl 3-methyl-1-phenyl-1H-pyrazolecarboxylate:** Ethyl 2-N-(methoxy)imino-4-oxopentanoate (0.5 g, 2.67 mmol) and phenylhydrazine (0.58 g, 5.35 mmol) in acetic acid (10 mL) and 2-methoxyethanol (5 mL) were heated at 105°C for 5h. The reation was evaporated, dissolved in ethyl acetate and washed with 0.2N HCl then water. The solution was dried (Na_2SO_4) evaporated and the residue applied to a silica gel column. Elution with a gradient of 10:1 to 5:1 hexane: ethyl acetate gave 160 mg of ethyl 3-methyl-1-phenyl-1H-pyrazolecarboxylate; LRMS $(M+H)^+$ m/z: 231.

[0064] **3-methyl-1-phenyl-1H-pyrazole-5-(N-(2'-N-t-butylaminosulfonyl-[1,1']-biphen-4-yl))carboxyamide:** To a

0°C of 4-(2-N-*t*-butylaminosulfonyl)phenyl)anilime (0.22 g, 0.73 mmol) in dichloromethane (10 mL) was added a solution of trimethylaluminum (2.0 M in hexane, 5 eq, 1.75 mL). This mixture was stirred for 15 min then ethyl 3-methyl-1-phenyl-1H-pyrazolecarboxylate (0.16 g, 0.69 mmol) in dichloromethane (5 mL) was added. The reaction was allowed to warm to ambient temperature and stirred for 18h.This mixture was carefully quenched with water, then diluted with ethyl acetate and the layers separated, dried and evaporated. The residue was applied to a silica gel column and the title compound isolated by gradient elution with mixture of 3:1 to 1:1 hexane:ethyl acetate. There was obtained 150 mg of 3-methyl-1-phenyl-1H-pyrazole-5-(N-(4-(2'-N-t-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxyamide; HRMS $(M+H)^+$ calc. m/z: 489.196038, obs: 489.194346.

[0065] 3-methyl-1-phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxyamide: A solution of 150 mg of 3-methyl-1-phenyl-1H-pyrazole-5-(N-(4-(2'-N-t-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxyamide in trifluoroacetic acid (15 mL) was heated at reflux for 1h. The reaction was evaporated, taken up in ethyl acetate and washed with 1N sodium hydroxide solution. The organic solution was dried and evaporated to give 140 mg of product. Further purification of 3-methyl-1-phenyl-1H-pyrazole-5-(N-(4-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide was effected by hplc utilizing gradient elution with a mixture of water: acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column; HRMS $(M+H)^+$ calc. m/z: 433.133438, obs: 433.131005.

EXAMPLE 2

3-Methyl-1-(2-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0066] This compound was prepared by the same methodology described for EXAMPLE 1 with 2-methoxyphenyl hydrazine · HCl substituted for phenyl hydrazine. There was obtained 3-methyl-1-(2-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide; HRMS $(M+H)^+$ calc. m/z: 463.144002, obs: 463.144162.

EXAMPLE 3

3-Methyl-1-(3-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0067] This compound was prepared by the same methodology described for EXAMPLE 1 with 3-methoxyphenyl hydrazine·HCl substituted for phenyl hydrazine. There was obtained 3-methyl-1-(2-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide; HRMS $(M+H)^+$ calc. m/z: 463.144002, obs: 463.144301.

EXAMPLE 4

3-Methyl-1-(4-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0068] This compound was prepared by the same methodology described for EXAMPLE 1 with 4-methoxyphenyl hydrazine·HCl substituted for phenyl hydrazine. There was obtained 3-methyl-1-(2-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide; HRMS $(M+H)^+$ calc. m/z: 463.144002, obs: 463.141980.

EXAMPLE 5

3-Methyl-1-(2-hydroxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0069] The product of EXAMPLE 2, 3-methyl-1-(2-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (0.245 g, 0.53 mmol), in dichloromethane (20 mL) was cooled to 0°C and a solution of borontribromide in dichloromethane (1.0 M, 6 equivalents, 3.2 mL) was added. The reaction was allowed to warm to ambient temperature and stirred for 18h. The reaction was evaporated and the residue allpied to a small plug of silica gel and eluted with ethyl acetate. The ethyl acetate solution was dried and evaporated. This material was purified by hplc utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column to give the title compound; HRMS $(M+H)^+$ calc. m/z: 449.128352, obs: 449.129006.

EXAMPLE 6

3-Methyl-1-(3-hydroxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0070] The product of EXAMPLE 3, 3-methyl-1-(3-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide was treated according to the procedure described for EXAMPLE 5 to give the title compound;

HRMS $(M+H)^+$ calc. m/z: 449.128352, obs: 449.127620.

EXAMPLE 7

3-Methyl-1-(4-hydroxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0071] The product of EXAMPLE 4, 3-methyl-1-(4-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide was treated according to the procedure described for EXAMPLE 5 to give the title compound; HRMS $(M+H)^+$ calc. m/z: 449.128352, obs: 449.127304.

EXAMPLE 8

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0072] 3-Methyl-1-(4-methoxyphenyl)-1H-pyrazolecarboxylic acid: A mixture of ethyl 3-methyl-1-(4-methoxyphenyl)-1H-pyrazolecarboxylate (0.01997 mol, 5.197 g) and potassium hydroxide (3.362 g, 3.0 eq.) in ethanol (70 mL) was stirred at ambient temperature for 5 h. The solvent was removed in vacuo and the residue was taken up in water. This was extracted with methylene chloride (3x) to remove unreacted starting material. The aqueous was made acidic (pH 3) by the dropwise addition of conc. HCl at 0°C to give white precipitation of acid. The solid acid was obtained by filtration and pumped on for several hours to dry. This procedure gave 4.23 g of pure product (91 %); mp: 161.8 °C.

[0073] 2-Fluoro-4-(2-aminosulfonylphenyl)aniline: A mixture of 2-fluoro-4-bromoaniline (0.01 mol, 2.51 g), boronic acid (2.57 g, 1.0 èq.), sodium carbonate (3.18 g, 3.0 eq.), and tetrakis(triphenylphosphine) palladium(0) (0.23 g, 0.02 eq.) in tetrahydrofuran(100 mL) and water (50 mL) was stirred at ambient temperature for 30 min. while nitrogen gas was bubbling to remove oxygen. This reaction mixture was then refluxed for 18 h. The reaction mixture was filtered through celite to remove catalyst and washed with tetrahydrofuran(50 mL). The filtrate was evaporated in vacuo and the residue was taken up in water then extracted with ethyl acetate (3x); the ethyl acetate extracts were washed with brine, dried ($MgSO_4$), and evaporated. This residue was purified by flash chromatography on a silica gel column (150 g) eluted with 2.5:1 hexane:ethyl acetate to give 1.976 g of pure product (61 %).

[0074] 3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-4-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide: To the solution of 3-methyl-1-(4-methoxyphenyl)-1H-pyrazolecarboxylic acid (0.001 mol, 0.232 g) in dry acetonitrile (10 mL) was added thionyl chloride (0.3 mL, 4.0 eq.). This reaction mixture was warmed up at 50°C for 1 h then allowed to cool to ambient temperature and stirred for 1h. The solvent and extra thionyl chloride were removed in vacuo and the residue was pumped on for several hours for further dry.

[0075] To this dried residue was added a mixture of 2-fluoro-4-((2-N-t-butylsulfonamido)phenyl)aniline (0.322 g, 1.0 eq.) and triethyl amine (0.14 mL, 1.0 eq.; 2.0 eq. for HCl salt) in dry methylene chloride (10 mL). This reaction mixture was allowed to stir at ambient temperature for 2 h. The reaction mixture was evaporated and purified by flash chromatography on a silica gel column(50 g) eluted with 3:1 hexane:ethyl acetate to give 0.301 g of pure product with t-butyl sulfonamide(56-%).

[0076] This product was treated with trifluoroacetic acid at 55°C for 2 h for deprotection of sulfonamide to give 0.287 g of pure product(86 %) after purification by reverse phase hplc; HUMS $(M+H)^+$ calc. 481.134581, found 481.133650 for the title compound.

EXAMPLE 9

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-bromo-4-(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide

[0077] 2-Bramo-4-(2 -aminosulfonylphenyl)aniline: This compound was prepared by the method described for 2-fluoro-4-(2-aminosulfonylphenyl)aniline described in EXAMPLE 8 by starting with 2,4-dibromoaniline rather than 2-fluoro-4-bromoaniline.

[0078] 3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-broano-4-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide: This compound was prepared by the same methods described for EXAMPLE 8 by coupling with 2-bromo-4-((2-N-t-butylsulfonamido)phenyl)aniline rather than 2-fluoro-4-((2-N-t-butylsulfonamido)phenyl)aniline. The title compound was obtained as pure product after purification by reverse phase hplc; HRMS $(M+H)^+$ calc. 541.054513, found 541.055340.

EXAMPLE 10

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-iodo-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0079] **2-Iodo-4-(2-aminosulfonylphenyl)aniline:** This compound was prepared by the method described for 2-fluoro-4-(2-aminosulfonylphenyl)aniline described in EXAMPLE 8 by starting with 2-iodo-4-bromoaniline rather than 2-fluoro-4-bromoaniline.

[0080] **3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-iodo-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide:** This compound was prepared by the same methods described for EXAMPLE 8 by coupling with 2-iodo-4-((2-N-t-butylsulfonamido)phenyl)aniline rather than 2-fluoro-4-((2-N-t-butylsulfonamido)phenyl)aniline. The title compound was obtained as pure product after purification by reverse phase hplc; HRMS $(M+H)^+$ calc. 589.040654, found 589.039223.

EXAMPLE 11

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-methyl-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0081] **2-Methyl-4-(2-aminosulfonylphenyl)aniline:** This compound was prepared by the method described for 2-fluoro-4-(2-aminosulfonylphenyl)aniline described in EXAMPLE 8 by starting with 2-methyl-4-bromoaniline rather than 2-fluoro-4-bromoaniline.

[0082] **3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-methyl-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide:** This compound was prepared by the same methods described for EXAMPLE 8 by coupling with 2-methyl-4-((2-N-t-butylsulfonamido)phenyl)aniline rather than 2-fluoro-4-((2-N-t-butylsulfonamido)phenyl)aniline. The title compound was obtained as pure product after purification by reverse phase hplc; HRMS $(M+H)^+$ calc. 477.159652, found 477.159337.

EXAMPLE 12

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-carboxyldimethylamine)phenyl)carboxyamide

[0083] **4-(N-Carboxyldimethylamine)aniline:** A 2-fold excess of neat dimethylamine (ca. 0.73 g) was added to a 0°C solution of p-nitrobenzoyl chloride (1.5 g, 8.1 mmol) in dichloromethane (50 mL). The reaction was then evaporated to dryness and the residue dissolved in ethyl acetate. This solution was washed with 1N hydrochloric acid solution and brine, then dried and evaporated to give 4-(N-carboxyldimethylamine)nitrobenzene.

[0084] This material was reduced under an atmosphere of hydrogen gas (50 psi) in methanol (100 mL) in the presence of 10% palladium on carbon catalyst (100 mg). After about 2 h, the reduction was complete; the reaction was purged with nitrogen gas and the catalyst removed by filtration through a pad of Celite. The solvent was evaporated to give the title compound.

[0085] **3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-carboxyldimethylamine)phenyl)carboxyamide:** This compound was prepared by the same methods described for EXAMPLE 8 by coupling with 4-(N-carboxyldimethylamine)aniline rather than 2-fluoro-4-((2-N-t-butylsulfonamido)phenyl)aniline and then omitting the final the trifloroacetic acid deprotection step. The title compound was obtained as pure product after purification by reverse phase hplc; HRMS $(M+H)^+$ calc. 379.177016, found 379.176235.

EXAMPLE 13

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-pyrrolidinocarbonyl)phenyl)carboxyamide

[0086] **4-(N-Pyrrolidinocarbonyl)aniline:** A 2-fold excess of neat pyrrolidine (1.15 g, 16.2 mmol) was added to a 0°C solution of p-nitrobenzoyl chloride (1.5 g, 8.1 mmol) in dichloromethane (50 mL). The reaction was then evaporated to dryness and the residue dissolved in ehtyl acetate. This solution was washed with 1N hydrochloric acid solution and brine, then dried and evaporated to give 4-(N-pyrrolidinocarbonyl)nitrobenzene.

[0087] This material was reduced under an atmosphere of hydrogen gas (50 psi) in methanol (100 mL) in the presence of 10% palladium on carbon catalyst (100 mg). After about 2 h, the reduction was complete; the reaction was purged with nitrogen gas and the catalyst removed by filtration through a pad of Celite. The solvent was evaporated to give the title compound.

[0088] **3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-pyrrolidinocarbonyl)phenyl)carboxyamide:** This compound was prepared by the same methods described for EXAMPLE 8 by coupling with 4-(N-pyrrolidinocarbonyl)

aniline rather than 2-fluoro-4-((2-N-t-butylsulfonamido)phenyl)aniline and then omitting the final the trifloroacetic acid deprotection step. The title compound was obtained as pure product after purification by reverse phase HPLC; HRMS $(M+H)^+$ calc. 404.184841, found 404.182119.

EXAMPLE 14

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-α-methyl-N-pyrrolidino)phenyl)carboxyamide

[0089] **4-(α-N-pyrrolidino)methyl aniline:** To pyrrolidine (0.67 g, 0.79 mL, 9.4 mmol) in chloroform (50 mL) was added 4-nitrobenzyl bromide (2.03 g, 9.4 mmol) and sodium carbonate (2 g). The reaction was heated at reflux for 2 h, then stirred at ambient temperature for 18 h. Water was added to the reaction mixture, then the layers were partitioned. The chloroform layer was dried and evaporated to give 1.55 g of N-alkylation product; LRMS $(M+H)^+$ m/z: 207.2.

[0090] Reduction of the nitro group on the material prepared above was effected by stirring this material with tin(II) chloride dihydrate (8.5 g, 37.6 mmol) in ethanol (50 mL) at ambient temperature for 18 h. The reaction was diluted with 1N sodium hydroxide solution and extracted with ethyl acetate (3x). The extracts were washed with brine, dried and evaporated to give 1.23 g of 4-(α-N-pyrrolidino)methyl aniline; LRMS $(M+H)^+$ m/z: 177.2.

[0091] **3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-α-methyl-N-pyrrolidino)phenyl)carboxyamide:** A mixture of 3-Methyl-1-(4-methoxyphenyl)-1H-pyrazolecarboxylic acid (100 mg, 0.43 mmol), 4-(α-N-pyrrolidino)methyl aniline (76 mg, 0.43 mmol) in dimethylformamide (3 mL) was cooled to 0°C. N-Methylmorpholine added. The reaction was allowed to thaw to ambient temperature and stirred for 18 h. The reaction was diluted with 1N sodium hydroxide, then extracted with ethyl acetate. The extracts were washed with brine, dried and evaporated. This material was purified by hplc utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column to give the title compound (70 mg); LRMS $(M+H)^+$ m/z: 391.2.

EXAMPLE 15

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0092] **3-Trifluoromethyl-5-methyl-1-(4-methoxyphenyl)-1H-pyrazole:** A mixture of 1,1,1-trifluoro-2,4-pentanedione (0.02 mol, 2.4 mL) and 4-methoxyphenyl hydrazine.HCl (4.54 g, 1.3 eq.) in 2-methoxyethanol (100 mL) and acetic acid (30 mL) was refluxed for 6 h. The reaction mixture was evaporated and purified by flash chromatography on a silica gel column (400 g) eluted with 4:1 hexane:ethyl acetate to give 4.5 g of pure product (88 %).

[0093] **3-Trifluoromathyl-5-hydroxymethyl-1-(4-methoxyphenyl)-1H-pyrazole:** A mixture of 3-trifluoromethyl-5-methyl-1-(4-methoxyphenyl)-1H-pyrazole (0.01756 mol, 4.5 g), N-bromosuccinimide (3.439 g, 1.1 eq.), and AIBN (0.1 g) in carbon tetrachloride (100 mL) was refluxed for 18 h. The reaction mixture was filtered through celite to remove solid impurity and washed with carbon tetrachloride (100 mL). The filtrate was evaporated and purified by flash chromatography on a silica gel column (400 g) eluted with 4:1 hexane:ethyl acetate to give 3.826 g of pure product (65%).

[0094] This material was treated with calcium carbonate (2.637 g, 1.5 eq.) in dioxane (80 mL) and water (20 mL) at 55-60°C for 18 h. The reaction mixture was evaporated and purified by flash chromatography on a silica gel column (400 g) eluted with 4:1 hexane:ethyl acetate to give 1.198 g of pure product (39 %). Recrystallization from a mixture of benzene:hexane gave an analytically pure sample; mp: 79.0 °C; CHNF: theory %C 52.95, %H 4.07, %N 10.29, %F 20.94; found %C 52.88; %H 3.98; %N 10.11; %F 20.62.

[0095] **3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid:** To the solution of 3-trifluoromethyl-5-hydroxymethyl-1-(4-methoxyphenyl)-1H-pyrazole (4.4007 mmol, 1.198 g) in acetonitrile (20 mL) and water (20 mL) was added sodium periodate (1.977, 2.1 eq.) and several crystals of ruthenium(III) chloride at 0°C. This reaction mixture was stirred at ambient temperature for 18 h. The reaction mixture was filtered through Celite to remove white solid impurity and the filter cake washed with 1:1 acetonitrile: water. The filtrate was evaporated in vacuo and the residue was taken up in water. The aqueous was made acidic (pH 3) by the dropwise addition of conc. HCl at 0°C then extracted with ethyl acetate (3x); the ethyl acetate extracts were washed with brine, dried ($MgSO_4$), and evaporated to gave 1.13 g of pure product (90 %).

[0096] **3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-N-t-butylaminossulfonyl-[1,1']-biphen-4-yl)carboxyamide:** To 300 mg of 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid (1.05 mmol) in dichloromethane (10 mL) at 0°C was added a solution of oxalyl chloride in dichloromethane (2M, 1.5 equivalents, 1.58 mmol, 0.8 mL) and a drop of dimethylformamide. After 4 h the reaction was complete, the solvent was evaporated and the acid chloride carried on to the next reaction.

[0097] The material prepared above was dissolved in dichloromethane (20 mL) and then added over a period of 15-20 min to a 0 °C solution of 4-(2-N-t-butylaminosulfonyl)phenyl)aniline (1.2 equivalents, 1.25 mmol, 0.365 g), pyridine (10 equivilents, 12.5 mmol, 0.99 g, 1.0 mL) and N,N-dimethylaminopyridine (1.2 equivilents, 1.25 mmol. 0.155 g)

in dichloromethane (20 mL). The reaction was maintained at 0 °C until thin layer chromatography indicated that all of the starting acid chloride was consumed. The reaction was evaporated, then the residue suspended in 1N hydrochloric acid solution. The suspension was extracted with ethyl acetate; the extracts were washed with 1N hydrochloric acid solution (2x) then dried and evaporated. There was obtained 660 mg of the desired product; LRMS $(M+Na)^+$ m/z: 594.5.

[0098] 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide: 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-N-t-butylaminosulfonyl-[1,1']-biphen-4-yl) carboxyamide (0.66 g) was dissolved in trifluoroacetic acid (20 mL) and heated at reflux for 30 min. The reaction was evaporated, then dissolved in ethyl acetate and washed with 1N sodium hydroxide solution (2x) and brine. This solution was dried and evaporated to 0.48 g of crude product. This material was made analytically pure by first subjecting it to flash chromatography with a 200 g column of silica gel and elution with 2:1 hexane:ethyl acetate and finally recrystallizing the homogeneous chromatography product from chloroform. There was obtained 0.262 g of the title compound; mp: 237.3; CHNSF: theory %C 55.81, %H 3.718, %N 10.85, %S 6.218, %F 11.03; found %C 56.02, %H 3.77, %N 10.51, %S 5.84, %F 11.29.

EXAMPLE 16

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-pyrrolidinocarbonyl)phenyl)carboxyamide

[0099] 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-pyrrolidinocarbonyl)phenyl)carboxyamide: 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid (500 mg) was dissolved in anhydrous CH_2Cl_2 (25 mL) with thionyl chloride (0.257 mL). This mixture was stirred at ambient temperature for 24 hours. The volatiles were removed under reduced pressure and the solution was dried under vacuum. 4-(N-Pyrrolidinocarbonyl) aniline (0.369 g) was dissolved in anhydrous CH_2Cl_2 30 mL) and cooled to 0°C. Anhydrous pyridine (1.43 mL), and DMAP (0.259 g) was added and the mixture was stirred for 15 minutes. The prepared acid chloride was dissolved in anhydrous CH_2Cl_2 (5 mL) and was added dropwise to the reaction mixture. The reaction was warmed to ambient temperature and stirred overnight. The mixture was concentrated in vacuo. Purification was done on silica gel using ethyl acetate:hexanes (1:1) as the eluent yielding 325 mg (95% purity by HPLC). LRMS $(M+H)^+ = 459$ $C_{23}H_{21}N_4O_3F_3$. HRMS for $C_{23}H_{21}N_4O_3F_3$ $(M+H)^+$ calc. 458.156576, found 458.156478. ^1H NMR ($CDCl_3$) δ 1.85-1.99 (m, 4H), 3.41 (t, 2H, J=6.23 Hz), 3.63 (t, 2H, J=6.59 Hz), 3.85 (s, 3H), 6.99 (d, 2H, J=6.95 Hz), 7.31 (s, 1H), 7.31 (s, 4H), 7.42 (d, 2H, J=6.59 Hz), 8.42 (s, 1H).

EXAMPLE 17

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-methanesulfonyl)phenyl)pyridin-2-yl) carboxyamide

[0100] 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-methanesulfonyl)phenyl)pyridin-2-yl) carboxyamide: This material was prepared according to the methods described for EXAMPLE 15 with the exception that during the coupling step 2-amino-5-(2-N-*t*-butylaminosulfonyl)phenyl)pyridine was substituted for 4-(2-N-*t*-butylaminosulfonyl)phenyl)aniline. Purification by hplc utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; LRMS $(M+H)^+$ m/z: 517, $(M+Na)^+$ m/z: 539.

EXAMPLE 18

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-N-pyrrolidinocarbonyl)pyridin-2-yl)carboxyamide

[0101] 2-Amino-5-(N-pyrrolidinocarbonyl)pyridine: A mixture of 2-aminonicotinic acid (2.26 g, 16.4 mmol) and pyrrolidine (1.16 g, 16.4 mmol) in dimethylformamide (20 mL) was cooled to 0°C. To the mixture was added N-methylmorpholine (3.31 g, 32.7 mmol) and HBTU (6.2 g, 16.4 mmol). The reaction was allowed to warm to ambient temperature and stirred 18 h. The reaction was diluted with 1N sodium hydroxide and extracted with ethyl acetate. The product was purified by flash chromatography using 10% methanol in chloroform as the eluent; 1.65 g of product was isolated; LRMS $(M+H)^+$ m/z: 192.

[0102] 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-N-pyrrolidinocarbonyl)pyridin-2-yl)carboxyamide: This material was prepared according to the methods described for EXAMPLE 15 with the exception that during the coupling step 2-amino-5-(N-pyrrolidinocarbonyl)pyridine was substituted for 4-(2-N-*t*-butylaminosulfonyl) phenyl)aniline. Purification by hplc utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; LRMS $(M+H)^+$ m/z: 460.2.

EXAMPLE 19

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-N-pyrrolidinocarbonyl)pyridin-2-yl)carboxyamide

[0103] **3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-N-pyrrolidinocarbonyl)pyridin-2-yl)carboxyamide**: To a solution of 3-methyl-1-(4-methoxyphenyl)-1H-pyrazolecarboxylic acid (1.02 g, 4.4 mmol) in dichloromethane (20 mL) at 0 °C was added 4.4 mL of a 2M solution of oxalyl chloride in dichloromethane followed by a drop of dimethylformamide. After 2 h the solvent was removed and 1.12 g of acid chloride was obtained. This material carried on to the next step without further purification.

[0104] To 2-amino-5-(N-pyrrolidinocarbonyl)pyridine (0.4 g, 2.1 mmol) with triethylamine (0.3 g, 3.0 mmol) in dichloromethane (40 mL) was added a dichloromethane (10 mL) solution of the acid chloride prepared above (0.5 g, 2.0 mmol). The reaction was allowed to thaw to ambient temperature and evaporated. The product was isolated by flash chromatoigraphy with 10% chloroform in methanol. Purification by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; HRMS $(M+H)^+$ calc. m/z: 405.180090, obs: 405.180328.

EXAMPLE 20

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-sulfonamido)phenyl)pyridin-2-yl)carboxyamide

[0105] This compound was prepared by the methodology described for EXAMPLE 19 with the exception that in the coupling step 2-amino-5-(2-(N-t-butylsulfonamido)phenyl)pyridine was used in the place of 2-amino-5-(N-pyrrolidinocarbonyl)pyridine. The resulting product was stirred in trifluoroacetic acid (20 mL) for 18 h, whereupon the solvent was removed by distillation under reduced pressure. Purification of the crude product by hplc utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; HRMS $(M+H)^+$ calc. m/z: 464.139251, obs: 464.138485.

EXAMPLE 21

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-3-hydroxypyrrolidino)phenyl)carboxyamide

[0106] **4-(N-Carboxyl-3-t-butyldimethylsilyloxypyrrolidino)aniline:** To 3-hydroxypyrrolidine hydrogen chloride (1.63 g, 14.9 mmol) and triethylamine (1.51 g, 14.9 mmol) in dichloromethane (50 mL) at 0°C, was added a solution of p-nitrobenzoyl chloride (2.5 g, 12.4 mmol) in dichloromethane (50 mL). The reaction was evaporated to dryness and the residue dissolved in ethyl acetate. This solution was washed with 1N hydrochloric acid solution and brine, then dried and evaporated to give 2.22 g of product; LRMS $(M+H)^+$ m/z: 237.

[0107] A tetrahydrofuran solution (75 mL) of the material prepared above (2.2 g, 9.4 mmol), t-butyldimethylsilyl chloride (1.54 g, 10.2 mmol) and imidazole (0.89 g, 13.0 mmol) was cooled to 0 °C and stirred for 72 h. The reaction mixture was filtered and evaporated. The residue was dissolved in ethyl acetate and washed with water and brine, dried and evaporated. Flash chromatography using 2:1 hexane:ethyl acetate gave 2.07 g of pure product; LRMS $(M+H)^+$ m/z: 351.

[0108] The material prepared above (2.07 g) was reduced under an atmosphere of hydrogen gas (50 psi) in methanol (100 mL) in the presence of 10% palladium on carbon catalyst (200 mg). After about 2 h, the reduction was complete; the reaction was purged with nitrogen gas and the catalyst removed by filtration through a pad of Celite. The solvent was evaporated to give 1.75 g of 4-(N-carboxyl-3-t-butyldimethylsilyloxypyrrolidino)aniline; LRMS $(M+H)^+$ m/z: 321.

[0109] **3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-3-hydroxypyrrolidino)phenyl)carboxyamide:** This compound was prepared by the methodology described for EXAMPLE 19 with the exception that in the coupling step 4-(N-carboxyl-3-t-butyldimethylsilyloxypyrrolidino) aniline was used in the place of 2-amino-5-(N-pyrrolidinocarbonyl)pyridine. The t-butyldimethylsilyl protecting group was removed by treatment with 2 equivalents of tetrabutylammonium fluoride in tetrahydrofuran. The solvent was evaporated, the residue dissolved in ethyl acetate and washed with water. After drying and removal of the solvent, the crude product was purified by hplc utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound;HRMS $(M+H)^+$ calc. m/z: 420.179756, obs: 420.175589.

EXAMPLE 37

1-(4-Methoxyphenyl)-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]tetrazole

[0110] **1-(4-Methoxyphonyl)-5-Carboethoxy-tetrazole:** 4-Methoxyaniline (20.0 g, 0.16 mol) and triethylamine (26.3

mL, 0.19 mol) were dissolved in CH_2Cl_2 (200 mL). Ethyl oxalyl chloride (18.1 mL, 0.16 mol) was added dropwise. The mixture was stirred at room temperature under N_2 for 15 min. It was diluted with CH_2Cl_2 and washed with water and brine. the CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated to a tan solid (34.7 g, 96%). MS (DCI-NH_3) 224, (M+H); 241, (M+NH_4).

[0111] The above amide (34.0 g, 0.15 mol) was refluxed for 20 h with a solution of triphenylphosphine (56.6 g, 0.22 mol) in 500 mL of CCl_4 (The solution was stirred at 0°C for 15 min before the amide was added). The reaction mixture was cooled and hexane was added. The precipitate was filtered off. The filtrate was concentrated to a solid. It was then dissolved in 400 mL of CH_3CN and NaN_3 (10.0 g, 0.15 mol) was added. The mixture was stirred at room temperature under N_2 for 12 h. The solvent was removed. The solid was dissolved in EtOAc and washed with water and brine. It was dried over $MgSO_4$ and concentrated, and chromatographed on silica gel(eluted with CH_2Cl_2) to give 27.7 g of the desired product (58%). MS(DCI-NH_3) 249, (M+H), 266 (M+NH_4)$^+$.

[0112] **1-(4-Methoxyphenyl)-5-[(2'-t-butylaminosulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]tetrazole:** 2'-t-Butylaminosulfonyl-4-amino-[1,1']-biphen-4-yl (1.84 g, 6.04 mmol) was dissolved in 100 mL of anhydrous CH_2Cl_2, and trimethylaluminium (15.2 mL of 2.0 M solution in heptane) was added slowly. The mixture was stirred at room temperature under N_2 for 15 min,and 1-(4-methoxyphenyl)-5-Carboethoxy-tetrazole (1.50 g, 6.04 mmol) was added. The reaction mixture was stirred at room temperature under N_2 for 18 h. The reaction was quenched carefully with 0.1N aqueous HCl. It was diluted with CH_2Cl_2 and washed with water and brine. The organic solution was then dried over $MgSO_4$, concentrated, and chromtographed on silica gel (10% EtOAc/CH_2Cl_2) to give 1.20 g of the desired product (39%). MS(ESI) 507.0 (M+H)$^+$.

[0113] **1-(4-Methoxyphenyl)-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]tetrazole:** 1-(4-Methoxyphenyl)-5-[(2'-t-butylaminosulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]tetrazole (1.20 g, 2.37 mmol) was dissolved in 10 mL of TFA. The mixture was refluxed under N_2 for h. The TFA was removed *in vacuo*. The crude mixture was purified by reversed phase HPLC to give 0.12 g of the desired product (11%). MS(ESI) 451.0 (M+H)$^+$.

EXAMPLE 38

3-Methyl-1-(4-methoxy-3-chloro)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0114] This compound was prepared by the same methodology described for EXAMPLE 1 with 4-methoxy-3-chlorophenyl hydrazine • HCl substituted for phenyl hydrazine. There was obtained 3-methyl-1-(4-trifluoromethyl)phenyl-1H-pyrazole-5-(N-(4-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide; HRMS (M+H)$^+$ calc. m/z: 497.1050, obs: 497.1045.

EXAMPLE 39

3-Methyl-1-(4-trifluoromethoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0115] This compound was prepared by the same methodology described for EXAMPLE 1 with 4-trifluoromethoxyphenyl hydrazine • HCl substituted for phenyl hydrazine. There was obtained 3-methyl-1-(4-trifluoromethyl)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide; HRMS (M+H)+ calc. m/z: 517.1170, obs: 517.1176.

EXAMPLE 40

1-(3-Bromophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0116] This compound was prepared by the same methodology described for EXAMPLE 1 with 3-bromophenyl hydrazine • HCl substituted for phenyl hydrazine. There was obtained 1-(3-bromophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide; HRMS(M+H)$^+$ calc. 511.043949; found: 511.043295.

EXAMPLE 41

1-(3-Iodophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0117] This compound was prepared by the same methodology described for EXAMPLE 1 with 3-iodophenyl hydrazine • HCl substituted for phenyl hydrazine. There was obtained 1-(3-iodophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide; HRMS(M+H)+ calc. 559.030090; found: 559.027878.

EXAMPLE 42

1-(3,4-Methylenedioxanephenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0118] This compound was prepared by the same methodology described for EXAMPLE 1 with 3,4-methylenedioxanephenyl hydrazine • HCl substituted for phenyl hydrazine. There was obtained 1-(3,4-methylenedioxanephenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide; HRMS(M+H)$^+$ calc. 477.123267; found: 477.124553.

EXAMPLE 43

1-(4-Methoxyphenyl)-3-hydroxylmethylene-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide

[0119] **1-(4-Methoxyphenyl)-3-hydroxylmethylene-18-pyrazole-5-ethylcarboxylate**: To a solution of 1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-5-ethylcarboxylate (1.58 g, 7.1 mmol) in CCl_4 (250 mL) was added NBS (1.5 g, 8.5 mmol) and benzoyl peroxide (73 mg, 4% mmol), and the mixture was degassed and then filled with nitrogen. After the mixture was refluxed for 18 hours under nitrogen, it was cooled to room temperature, diluted with CH_2Cl_2 (100 mL), washed with 10% NaOH (20 mL X 3), water (20 mL x 3), and brine (10 mL x 2), and dried over $MgSO_4$. Filtration and concentration gave a crude bromide (2.4 g). To a solution of the crude bromide in aqueous DMSO (75%, 40 mL) was added Cu_2O (1.5 g, 10.5 mmol), and the mixture was stirred at 60°C for 2 hours. The mixture was filtered to remove excess Cu_2O, and the filtrate was extracted with ethyl ether. The ether layer was washed with brine (10 mL x 5) and dried over $MgSO_4$. Filtration and concentration, followed by purification by flash chromatography with EtOAc-CH_2Cl_2 (1 to 1) gave 1-(4-methoxyphenyl)-3-hydroxylmethylene-1H-pyrazole-5-ethylcarboxylate (1.5 g, 81%). LRMS (M+H)$^+$ m/z: 277. **1-(4-Methoxyphenyl)-3-hydroxylmethylene-1H-pyrazole-5-(4'-pyrrolidincarbonyl)anilide**: To a solution of 4-(4'-pyrrolidinoncarbonyl)aniline (390 mg, 2.05 mmol) in CH_2Cl_2 (20 mL) was added $AlMe_3$ (2M in hexanes, 3 mmol) at 0°C. After the mixture was stirred at room temperature for 15 minutes, to it was added a solution of 1-(4-methoxyphenyl)-3-hydroxylmethylene-1H-pyrazole-5-ethylcarboxylate (560 mg, 2.05 mmol) in CH_2Cl_2 (5 mL), and the resulting mixture was stirred overnight. The mixture was quenched with water (5 mL), and filtered through a pad of Celite to remove $Al(OH)_3$. The filtrate was washed with water and brine, and dried over $MgSO_4$. Filtration, concentration, and purification by flash chromatography with EtOAc-CH_2Cl_2 gave 1-(4-methoxyphenyl)-3-hydroxylmethylene-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide (570 mg, 67% yield). ESMS (M+Na)$^+$ m/z: 443. HRMS (M+H)+ calc. m/z: 420.1798, obs: 420.1771.

EXAMPLE 44

1-(4-Methoxyphenyl)-3-formaldehyde-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide

[0120] To a solution of 1-(4-methoxyphenyl)-3-hydroxylmethylene-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide (140 mg, 0.33 mmol) in THF (20 mL) was added MnO_2 (435 mg, 15 eq.), and the resulting mixture was refluxed for 12 hours. The mixture was filtrated to remove excess MnO_2, and the filtrate was concentrated to give 1-(4-methoxyphenyl)-3-formaldehyde-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide as a solid in almost quantitative yield. LRMS (M+H)$^+$ m/z: 419.

EXAMPLE 45

1-(4-Methoxyphenyl)-5-(4'-pyrrolidinocarbonyl)anilide-3-pyrazolecarboxylic acid

[0121] To a solution of $AgNO_3$ (34 mg, 0.2 mmol) in H_2O (0.5 mL) was added NaOH (16 mg, 0.4 mmol), and then was added a solution of 1-(4-methoxyphenyl)-3-formaldehyde-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide (42 mg, 0.1 mmol) in MeOH (0.5 mL) at 0°C. After the resulting mixture was stirred at room temperature for 30 minutes, the mixture was carefully acidified with conc. HCl (35 μL) to pH ~ 2, and concentrated to give a residue, which was purified by flash chromatography to give 1-(4-methoxyphenyl)-5-(4'-pyrrolidinocarbonyl)anilide-3-pyrazolecarboxylic acid (25 mg, 58%). ESMS (M+Na)$^+$ m/z: 456.9.

EXAMPLE 4 6

1-(4-Methoxyphenyl)-3-methylcarboxylate-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide

[0122] To a solution of 1-(4-methoxyphenyl)-3-formaldehyde-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide (42 mg, 0.1 mmol) in MeOH (1 mL) was added KCN (7.8 mg, 0.12 mmol), HOAc (7.2 mg, 0.12 mmol) and MnO_2 (120 mg, 0.83 mmol), and the resulting mixture was stirred ar r.t. for 12 hours. The mixture was diluted with EtOAc (50 mL), washed with water (10 mL x 3) and brine, and dried over $MgSO_4$. The solution was filtrated, concentrated, and purified by flash chromatography with EtOAc gave 1-(4-methoxyphenyl)-3-methylcarboxylate-1H-pyrazole-5-(4'-pyrrolidinocarbonyl) anilide (38 mg, 85% yield). ESMS $(M+Na)^+$ m/z: 471.

EXAMPLE 47

1-(4'-Chlorophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0123] This compound was prepared by the same methodology described for EXAMPLE 1 with 4-chlorophenyl hydrazine • HCl substituted for phenyl hydrazine. There was obtained 1-(4'-chlorophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide; HRMS $(M+H)^+$: calc. 467.094465; found 467.093532.

EXAMPLE 48

1-(4'-Chlorophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1-pyridyl-1'-phenyl]-4-yl)carboxyamide

[0124] This compound was prepared by the same methodology described for EXAMPLE 8 with 4-chlorophenyl hydrazine • HCl substituted for phenyl hydrazine and 2-amino-5-(2-N-t-butylaminosulfonylphenyl)pyridine was used in the coupling step. There was obtained the title compound; HRMS $(M+H)^+$: calc. 468.089714; found 468.088873.

EXAMPLE 49

1-(3',4'-Dichlorophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0125] This compound was prepared by the same methodology described for EXAMPLE 1 with 3,4-dichlorophenyl hydrazine • HCl substituted for phenyl hydrazine. There was obtained the title compound; HRMS $(M+H)^+$: calc. 501.055493; found 501.053920.

EXAMPLE 50

1-(3'-Chlorophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0126] This compound was prepared by the same methodology described for EXAMPLE 1 with 3-chlorophenyl hydrazine • HCl substituted for phenyl hydrazine. There was obtained the title compound; HRMS $(M+H)^+$: calc. 467.094465; found 467.091517.

EXAMPLE 57

N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylthio)pyrazole-5-carboxyamide

[0127] **Ethyl N-(4-methoxyphenyl)glycine:** To a solution of 15.00 g (122 mmol) of p-anisidine in 100 mL of DMF under N_2 was added 23.50 g (141 mmol) of ethyl bromoacetate and 14.95 g (141 mmol) anhydrous sodium carbonate. The mixture was heated to 70°C for 16 hours and then cooled to room temperature. Water (500 mL) was added and the mixture stirred vigorously until a precipitate formed. The solid was collected and washed with 100 mL water, then dried *in vacuo* to give 19.59 g (88%) of the desired compound as a grey solid. ^1H NMR ($CDCl_3$): δ 6.81 (d, J = 8.8, 2H); 6.579 (d, J = 8.8, 2H); 4.24 (q, J = 7.0, 2H); 4.10 (s, 1H); 3.86 (s, 2H); 3.75 (s, 3H); 1.28 (t, J = 7.0, 3H).

[0128] **N-(4-Methoxyphenyl)glycine:** To a solution of 19.59 g (108 mmol) of ethyl N-(4-methoxyphenyl)glycine in 100 mL of THF under N_2 was added 5.44 g (130 mmol) of lithium hydroxide monohydrate in 25 mL water. After 15 hours, the mixture was reduced to 1/2 the original volume in vacuo and then acidified with concentrated hydrochloric acid to ph 3 and a precipitate formed. The solid was collected and washed with 100 mL water, then dried *in vacuo* to give 9.92 g (51%) of the desired compound as a off-white solid. ^1H NMR ($CDCl_3$): δ 6.68 (d, J = 8.8, 2H); 6.49 (d, J =

8.8, 2H); 3.73 (s, 2H); 3.64 (s, 3H); 2.49 (br s, 2H).

[0129] N-(4-Methoxyphenyl)-N-nitrosoglycine: Sodium nitrite (3.97 g, 57.5 mmol) in 10 mL of water was added to a suspension of N-(4-methoxyphenyl)glycine (9.92 g, 54.7 mmol) in 50 mL of water under N_2. This was allowed to stir at room temperature until solution clarified, about 6 hours. The solution was acidified with concentrated hydrochloric acid to pH 3 and a precipitate formed. The solid was collected and washed with 50 mL water, then dried *in vacuo* to give 11.50 g (100%) of the desired compound as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.17 (d, J = 8.8, 2H); 6.70 (d, J = 8.8, 2H); 4.30 (s, 2H), 3.56 (s, 3H), 2.29 (br s, 1H).

[0130] 1-(4-Methoxyphenyl)-4-oxy-1,2,3-oxadiazole: N-(4-methoxyphenyl)-N-nitrosoglycine (11.50 g, 54.7 mmol) was dissolved in 100 mL of acetic anhydride and heated to 70°C for 14 hours. The reaction mixture was cooled and then poured into 300 mL of ice-water. After stirring for 30 minutes to decompose the excess acetic anhydride, the reaction mixture was filtered to provide 10.50 g (100%) of a clear, thick oil. ^{1}H NMR ($CDCl_3$): δ 7.65 (d, J = 9.2, 2H), 7.08 (d, J = 9.2, 2H), 6.63 (s, 1H), 3.91 (s, 3H). MS (NH_3-Cl) m/z 193.3 $(M+H)^+$. **1-(3-Cyanophenyl)-4-oxy-5-methylthio-1,2,3-oxadiazole:** 1-(4-methoxyphenyl)-4-oxy-1,2,3-oxadiazole (2.03 g, 10.6 mmol) was dissolved in 26 mL of dry DMSO and cooled to 0°C. Acetyl chloride (1.66 g, 21.1 mmol) was added very slowly via syringe below the surface of the liquid under N_2. The reaction mixture was allowed to stir at room temperature for 14 hours. The reaction mixture was diluted with 100 mL Et_2O and washed twice with 25 mL saturated aqueous $NaHCO_3$ then three times with 25 mL water to remove the DMSO. The organic extract was dried with $MgSO_4$ and concentrated in vacuo to give 1.83 g of a red solid which was used without further purification. MS (NH_3-Cl) m/z 239.2 $(M+H)^+$.

[0131] Methyl 1-(4-methoxyphenyl)-3-methylthio-pyrazole-5-carboxylate: The crude 1-(4-methoxyphenyl)-4-oxy-5-methylthio-1,2,3-oxadiazole (1.83 g, 7.68 mmol) and methyl propriolate (6.45 g, 76.8 mmol) were dissolved in 10 mL of CH_2Cl_2 and the quartz reaction vessel purged with N_2. The reaction mixture was irradiated in a Rayonet RPR-100 photochemical reactor for 14 hours. The crude product was concentrated in vacuo and then chromatographed with 20% EtOAc/hexanes on silica to provide 1.06 g (49%) of a yellow solid. ^{1}H NMR ($CDCl_3$) : δ 7.33 (d, J = 8.8, 2H); 6.95 (d, J = 8.8, 2H); 6.89 (s, 1H); 3.85 (s, 3H); 3.78 (s, 3H); 2.55 (s, 3H). MS (NH_3-Cl) m/z 279.2 $(M+H)^+$.

[0132] N-(2'-t-Butylaminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-methylthio-pyrazole-5-carboxamide: Trimethyl aluminum (1.4 mL, 2.0 M in heptane, 2.8 mmol) was added to 2'-t-butylaminosulfonyl-4-amino-[1,1'] biphen-4-yl (215 mg, 0.71 mmol) in CH_2Cl_2 (5 mL). After stirring at room temp under N_2 for 75 minutes, a solution of methyl 1-(4-methoxyphenyl)-3-methylthio-pyrazole-5-carboxylate (197 mg, 0.71 mmol) in CH_2Cl_2 (2 mL) was added and the resulting solution stirred 70 hours. The reaction was quenched carefully by dropwise addition of 1M HCl, diluted with H_2O, and extracted into CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The crude product was chromatographed on silica gel (30-40% EtOAc/hexanes) to yield the desired product (357 mg, 92%). ^{1}H NMR ($CDCl_3$): δ 8.14 (d, 1H, J = 7.7), 7.50 (m, 9H) , 7.27 (m, 1H) , 7.01 (d, 2H, J = 8.8), 6.83 (s, 1H), 3.87 (s, 3H), 3.57 (s, 1H), 2.59 (s, 3H), 1.01 (s, 9H).

[0133] N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-methylthio-pyrazole-5-carboxamide: N-(2'-t-butylaminosulfonyl-[1,1']biphen-4-yl)-1-(4-methoxyphenyl)-3-methylthio-pyrazole-5-carboxamide (328 mg, 0.60 mmol) was stirred in TFA (5 mL) for 17 hours. The solvent was evaporated and the crude product chromatographed on silica gel (50% EtOAc/hexanes) to yield a yellow solid (267 mg, 91%). ^{1}H NMR ($CDCl_3$): δ 10.62 (s, 1H), 7.98 (dd, 1H, J = 7.7, J' = 1.5), 7.62 (d, 2H, J = 8.8), 7.55 (m, 2H), 7.30 (m, 5H), 7.22 (s, 2H), 6.98 (m, 3H), 3.76 (s, 3H), 2.51 (s, 3H).

EXAMPLE 58

1-(4-Methoxyphenyl)-3-(methylsulfonyl)-N-(5-(2'-methylsulfonylphenyl)pyrimid-2-yl)pyrazole-5-carboxamide

[0134] 2-Methylthiophenylboronic acid: 2-Bromothioanisole (29.0 g, 143 mmol) was dissolved in dry THF (400 mL) and cooled to -75°C. n-BuLi (62.0 mL, 2.5 M in hexane, 155 mmol) was added over 50 minutes. After stirring 25 minutes, triisopropyl borate (46 mL, 199 mmol) was added over 35 minutes. The cold bath was removed and the reaction was stirred at room temp for 16 hours. The resulting solution was cooled in an ice bathours, and 6 M HCl (100 mL) was added. This mixture was stirred at room temp 5 hours and concentrated to about half of the original volume. The concentrated solution was partitioned between Et_2O and water. The organic layer was extracted with 2 M NaOH, which was subsequently reacidified with 6 M HCl and extracted several times back into Et_2O. These Et_2O washes were dried over Na_2SO_4, filtered, and evaporated to yield a beige solid (20.4 g, 85%). ^{1}H NMR ($CDCl_3$): δ 8.01 (dd, 1H, J = 7.3, J' = 1.4), 7.53 (dd, 1H, J = 7.7, J' = 1.1), 7.43 (td, 1H, J = 7.3, J' = 1.8), 7.34 (td, 1H, J = 7.3, J' = 1.5), 6.22 (s, 2H), 2.50 (s, 3H).

[0135] 2-[Bis(tert-butoxycarbonyl)amino]-5-bromopyrimidine: Sodium hydride (5.06 g, 60%, 127 mmol) was added in 2 portions to 2-amino-5-bromopyrimidine (10.0 g, 57 mmol) in dry THF (500 mL) at 0°C. After stirring 30 minutes, di-*t*-butyl dicarbonate (27.6 g, 126 mmol) was added. The resulting mixture was refluxed 17 hours, quenched carefully with water, and concentrated. The concentrated mixture was diluted with EtOAc and extracted with water. The combined aqueous layers were extracted with EtOAc. All of the organic layers were combined, dried over Na_2SO_4,

filtered, and evaporated. The crude product was chromatographed on silica gel (10-15% EtOAc/hexanes) to yield the desired product (15.48 g, 72%). ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 2H), 1.47 (s, 18H).

[0136] 2-[Bis(tert-butoxycarbonyl)amino]-5-(2'-methylthiophenyl) pyrimidine: 2-[Bis(tert-butoxycarbonyl)amino]-5-bromopyrimidine (2.00 g, 5.3 mmol) was dissolved in benzene (130 mL). 2-methylthiophenylboronic acid (2.24 g, 13.3 mmol), aq. sodium carbonate (13 mL, 2.0 M, 26 mmol), tetrabutyl ammonium bromide (86 mg, 0.26 mmol), and bis(triphenylphosphine)palladium(II)chloride (190 mg, 0.27 mmol) were added, and the resulting mixture was first purged with vacuum and argon, then refluxed 17 hours. The cooled mixture was diluted with EtOAc and water. The layers were separated, and the organic was dried over Na_2SO_4, filtered, and evaporated. The crude product was chromatographed on silica gel (50% EtOAc/hexanes), evaporated, and chromatographed a second time on silica gel (30-50% EtOAc / hexanes) to yield the desired product (2.13 g, 96%). ^{1}H NMR ($CDCl_3$): δ 8.81 (s, 2H), 7.41 (m, 2H), 7.25 (m, 2H), 2.39 (s, 3H), 1.49 (s, 18H).

[0137] 2-[Bis(tert-butoxycarbonyl)amino]-5-(2'-methylsulfonylphenyl) pyrimidine: 2-[Bis(tert-butoxycarbonyl) amino]-5-(2'-methylthiophenyl)pyrimidine (2.13 g, 5.1 mmol) was dissolved in MeOH (20 mL) and cooled to 0°C. In a separate beaker, a solution of Oxone (5.49 g) was generated by dilution to 27 mL with water. A portion of this solution (17 mL, 5.6 mmol) was removed and adjusted to pH 4.2 with sat. Na_3PO_4 solution (4.7 mL). This mixture was added to the reaction and stirred 23 hours at room temp. The resulting mixture was diluted with water and extracted with $CHCl_3$. The organics were combined, washed with water and brine, dried over Na_2SO_4, filtered, and evaporated. The crude product was chromatographed on silica gel (50-100% EtOAc/hexanes) to yield the sulfone (1.28 g, 56%). ^{1}H NMR ($CDCl_3$): δ 8.81 (s, 2H), 8.28 (dd, 1H, J = 7.6, J' = 1.4), 7.72 (m, 2H), 7.39 (dd, 1H, J = 7.3, J' = 1.4), 2.76 (s, 3H), 1.50 (s, 18H).

[0138] 2-Amino-5-(2'-methylsulfonylphenyl)pyrimidine hydrochloride: 2-[Bis(tert-butoxycarbonyl)amino]-5-(2'-methylsulfonylphenyl) pyrimidine (1.28 g, 2.8 mmol) was suspended in HCl/dioxane (10 mL, 4.0 M) and stirred 20 hours at room temp. The resulting mixture was triturated with Et_2O and filtered to yield a white solid (772 mg, 95%). ^{1}H NMR ($CDCl_3$ + few drops MeOD): δ 8.53 (s, 2H), 8.22 (dd, 1H, J = 7.7, J' = 1.8), 7.77 (m, 2H), 7.40 (dd, 1H, J = 7.4, J' = 1.5), 2.94 (s, 3H).

[0139] Methyl 1-(4-methoxyphenyl)-3-methylsulfonyl-pyrazole-5-carboxylate: M-CPBA (1.18 g, 57-86%, minutes. 3.9 mmol) was added to methyl 1-(4-methoxyphenyl)-3-methylthio-pyrazole-5-carboxylate (434 mg, 1.6 mmol) in CH_2Cl_2 (40 mL) and stirred at room temperature for 24 hours. Additional m-CPBA (600 mg, 57-86%, minutes. 1.9 mmol) was added and stirred 2.5 days. The reaction was extracted with saturated Na_2SO_3 and saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The crude product was chromatographed on silica gel (40% EtOAc/hexanes) to yield the desired product (416 mg, 86%). ^{1}H NMR ($CDCl_3$): δ 7.46 (s, 1H) , 7.36 (d, 2H, J = 8.8), 6.99 (d, 2H, J = 8.8), 3.87 (s, 3H), 3.84 (s, 3H), 3.26 (s, 3H).

[0140] 1-(4-Methoxyphenyl)-3-methylsulfonyl-pyrazole-5-carboxylic acid: A solution of lithium hydroxide (1.3 mL, 1.0 M, 1.3 mmol) was added to a suspension of methyl 1-(4-methoxyphenyl)-3-methylsulfonyl-pyrazole-5-carboxylate (272 mg, 0.88 mmol) in MeOH (10 mL) and stirred at room temperature 17 hours. The resulting mixture was concentrated and partitioned between EtOAc and H_2O. The organic extracted was removed, and the aqueous extract was acidified with 1M HCl and extracted twice with EtOAc. The organic extracts from this extraction were combined, dried over Na_2SO_4, filtered, and evaporated to yield product (266 mg). ^{1}H NMR ($CDCl_3$ + few drops MeOD): δ 7.45 (s, 1H), 7.38 (d, 2H, J = 9.2), 6.96 (d, 2H, J = 9.2), 3.86 (s, 3H), 3.25 (s, 3H).

[0141] 1-(4-Methoxyphenyl)-3-(methylsulfonyl)-N-(5-(2'-methylsulfonylphenyl)pyrimid-2-yl)pyrazole-5-carboxamide: Oxalyl chloride (120 µl, 1.4 mmol) and dry DMF (2 drops) were added at room temperature to 1-(4-methoxyphenyl)-3-methylsulfonyl-pyrazole-5-carboxylic acid (262 mg, 0.88 mmol) in dry CH_2Cl_2 (5 mL) and stirred 2 hours under N_2. The resulting solution was evaporated and placed briefly under high vacuum before redissolving in CH_2Cl_2 (2 mL). This solution was added over a few minutes to a mixture of 2-amino-5-(2'-methylsulfonylphenyl)pyrimidine hydrochloride (253 mg, 0.89 mmol) and 4-dimethylaminopyridine (270 mg, 2.2 mmol) in CH_2Cl_2 (3 mL). The resulting solution was stirred at room temperature under N_2 for 23 hours, diluted with CH_2Cl_2, extracted with H_2O, dried over Na_2SO_4, filtered, and evaporated. The crude product was chromatographed on silica gel (75-100% EtOAc/hexanes) to yield an impure white solid, which was taken up in toluene and filtered to yield clean product (191 mg, 41%). ^{1}H NMR ($CDCl_3$): δ 8.65 (s, 2H), 8.62 (s, 1H), 8.24 (d, 1H, J = 7.0), 7.71 (m, 2H), 7.47 (d, 2H, J = 8.8), 7.39 (s, 1H), 7.33 (d, 1H, J = 6.6), 6.98 (d, 2H, J = 8.8), 3.85 (s, 3H), 3.30 (s, 3H), 2.80 (s, 3H).

EXAMPLE 59

N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazole-5-carboxamide

[0142] N-(2'-t-Butylaminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazole-5-carboxamide: Trimethyl aluminum (930 µl, 2.0 M in heptane, 1.86 mmol) was added to 2'-t-butylaminosulfonyl-4-amino-[1,1']biphen-4-yl (142 mg, 0.47 mmol) in CH_2Cl_2 (5 mL). After stirring at room temperature under N_2 for 60

minutes, a solution of methyl 1-(4-methoxyphenyl)-3-methylsulfonyl-pyrazole-5-carboxylate (145 mg, 0.47 mmol) in CH_2Cl_2 (2 mL) was added and the resulting solution stirred for 51 hours. The reaction was quenched carefully by dropwise addition of 0.1 M HCl, diluted with H_2O, and extracted twice into CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated to yield the desired product (277 mg, 100%). ^1H NMR ($CDCl_3$): δ 8.21 (bs, 1H), 8.16 (dd, 1H, J = 7.6, J' = 1.1), 7.57 (m, 3H), 7.46 (m, 5H), 7.39 (s, 1H), 7.27 (d, 1H, J = 7.3), 6.99 (d, 2H, J = 8.8), 3.86 (s, 3H), 3.31 (s, 3H), 1.03 (s, 9H).

[0143] N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazole-5-carboxamide: N-(2'-t-butylamino-sulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)pyrazole-5-carboxamide (274 mg, 0.47 mmol) was stirred in TFA (5 mL) for 74 hours. The solvent was evaporated. The crude product was recrystallized from $CHCl_3$ to yield a white solid (236 mg, 95%). ^1H NMR ($CDCl_3$ + few drops MeOD): δ 8.13 (d, 1H, J = 7.7), 7.67 (d, 2H, J = 8.4), 7.59 (t, 1H, J = 6.3), 7.46 (m, 6H), 7.32 (d, 1H, J = 8.5), 7.00 (d, 2H, J = 9.2), 3.86 (s, 3H), 3.31 (s, 3H).

EXAMPLE 60

N-(4-Benzoylpyrrolidino)-1-(4-methoxyphenyl)-3-(methylthio)-1H-pyrazole-5-carboxamide

[0144] 1-(4-Methoxyphenyl)-3-methylthio-1H-pyrazole-5-carboxylic acid: A solution of lithium hydroxide (4.5 mL, 1.0 M, 4.5 mmol) was added to a suspension of methyl 1-(4-methoxyphenyl)-3-methylthio-1H-pyrazole-5-carboxylate (840 mg, 3.0 mmol) in MeOH (30 mL) and stirred at room temperatureerature for 21 hours. The resulting mixture was concentrated and partitioned between EtOAc and H_2O. The organic layer was removed, and the aqueous layer was acidified with 1M HCl and extracted twice with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated to yield clean product (784 mg, 99%). ^1H NMR ($CDCl_3$): δ 7.33 (d, 2H, J = 8.4), 6.97 (s, 1H), 6.95 (d, 2H, J = 8.4), 3.85 (s, 3H), 2.55 (s, 3H).

[0145] N-(4-Benzoylpyrrolidino)-1-(4-methoxyphenyl)-3-(methylthio)-1H-pyrazole-5-carboxamide: Oxalyl chloride (140 µl, 1.6 mmol) and dry DMF (2 drops) were added at room temperature to 1-(4-methoxyphenyl)-3-methylthio-1H-pyrazole-5-carboxylic acid (275 mg, 1.0 mmol) in dry CH_2Cl_2 (8 mL) and stirred for 100 minutes under N_2. The resulting solution was evaporated and placed briefly under high vacuum before redissolving in CH_2Cl_2 (8 mL). (4-aminobenzoyl)pyrrolidine (198 mg, 1.0 mmol) was added, followed by 4-dimethylaminopyridine (190 mg, 1.6 mmol). The resulting mixture was stirred at room temperature for 17 hours, diluted with CH_2Cl_2, and extracted with H_2O. The aqueous extract was extracted with CH_2Cl_2, the combined organic extracts were extracted with brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The crude product was chromatographed on silica gel (75-100% EtOAc/hexanes) to yield the desired product (464 mg, 100%). ^1H NMR ($CDCl_3$): δ 7.91 (bs, 1H), 7.44 (s, 4H), 7.39 (d, 2H, J = 8.8), 6.97 (d, 2H, J = 8.8), 6.83 (s, 1H), 3.84 (s, 3H), 3.62 (t, 2H, J = 6.6), 3.42 (t, 2H, J = 6.6), 2.57 (s, 3H), 1.91 (m, 4H).

EXAMPLE 61

1-(4-Methoxyphenyl)-N-(5-(2'-methylsulfonylphenyl)pyrimid-2-yl)-3-(methylthio)-1H-pyrazole-5-carboxamide

[0146] 1-(4-Methoxyphenyl)-N-(5-(2'-methylsulfonylphenyl)pyrimid-2-yl)-3-(methylthio)-1H-pyrazole-5-carboxamide: Trimethyl aluminum (1.5 mL, 2.0 M in heptane, 3.0 mmol) was added to 2-amino-5-(2'-methylsulfonylphenyl)pyrimidine hydrochloride (208 mg, 0.73 mmol) in CH_2Cl_2 (5 mL). After stirring at room temperature under N_2 for 75 minutes, a solution of methyl 1-(4-methoxyphenyl)-3-methylthio-1H-pyrazole-5-carboxylate (203 mg, 0.73 mmol) in CH_2Cl_2 (2 mL) was added and the resulting solution stirred for 70 hours. The reaction was quenched carefully by dropwise addition of 1M HCl, diluted with 1M HCl, and extracted into CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The crude product was chromatographed on silica gel (50-100% EtOAc/hexanes) to yield the desired product (101 mg, 28%). This material was combined with 19 mg from another reaction and purified by preparative HPLC on a C-18 reversed-phase column (30-100% MeCN/H_2O/0.05% TFA) to yield a white powder (111 mg). ^1H NMR ($CDCl_3$): δ 8.67 (s, 2H), 8.24 (d, 1H, J = 7.3), 7.71 (m, 2H), 7.44 (d, 2H, J = 9.1), 7.33 (d, 1H, J = 8.4), 6.96 (d, 2H, J = 9.2), 6.86 (s, 1H), 3.84 (s, 3H), 2.79 (s, 3H), 2.59 (s, 3H).

EXAMPLE 62

N-(4-Benzoylpyrrolidino)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazole-5-carboxamide

[0147] N-(4-Benzoylpyrrolidino)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazole-5-carboxamide: N-(4-benzoylpyrrolidino)-1-(4-methoxyphenyl)-3-(methylthio)-1H-pyrazole-5-carboxamide (200 mg, 0.46 mmol) was

dissolved in MeOH (6 mL). A solution of Oxone (561 mg, 0.91 mmol) in H_2O (3 mL) was added, and the resulting mixture stirred at room temperature under Ar for 17 hours. The reaction was diluted with H_2O and extracted twice with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by preparative HPLC on a C-18 reversed-phase column (10-70% MeCN/H_2O/0.05% TFA) to yield a white powder (200 mg, 93%). ^1H NMR ($CDCl_3$): δ 8.98 (s, 1H), 7.52 (s, 1H), 7.39 (m, 6H), 6.95 (d, 2H, J = 8.8), 3.84 (s, 3H), 3.65 (t, 2H, J = 6.6), 3.41 (t, 2H, J = 6.2), 3.28 (s, 3H), 1.93 (m, 4H).

EXAMPLE 63

N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methoxymethyl)-1H-pyrazole-5-carboxamide

[0148] Ethyl 3-(bromomethyl)-1-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate and ethyl 3-(dibromomethyl)-1-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate: Ethyl 1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-5-carboxylate (2.00 g, 7.83 mmol) was dissolved in 30 mL CCl_4 and N-bromosuccinimide (3.06 g, 17.2 mmol) and benzoylperoxide (0.02 g, 0.08 mmol) were added. The reaction mixture was heated for 48 hours then cooled to room temperature. The succinimide was filtered away and the solvent evaporated. The reaction mixture was chromatographed on silica (20% EtOAc/hexanes) to give the 0.94 g (36%) of the monobromide. ^1H NMR ($CDCl_3$): δ 7.34 (d, J = 8.8, 2H); 7.06 (s, 1H); 6.96 (d, J = 8.8, 2H); 4.53 (s, 2H); 4.24 (q, J = 7.0, 2H); 3.85 (s, 3H); 1.27 (t, J = 7.0, 3H). The dibromide (0.34 g, 10%) was also isolated. ^1H NMR ($CDCl_3$): δ 7.34 (d, J = 9.1, 2H); 7.31 (s, 1H); 6.96 (d, J = 9.1, 2H); 6.73 (s, 1H); 4.26 (q, J = 7.0, 2H); 3.85 (s, 3H); 1.29 (t, J = 7.0, 3H).

[0149] 1-(4-Methoxyphenyl)-3-(methoxymethyl)-1H-pyrazole-5-carboxylic acid: Ethyl 3-(bromomethyl)-1-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate (0.50 g, 1.47 mmol) is dissolved in 12 mL of 0.5 M NaOMe in methanol and heated to reflux for 14 hours. The reaction mixture was cooled and reduced to 1/10 original volume. The reaction mixture was dissolved in 20 mL of water and extracted with EtOAc. The aqueous mixture was acidified with 1N HCl and extracted with EtOAc to give 0.236 g (61%) of desired product. A mixture of ethyl and methyl esters (~ 0.05 g) was found in the first EtOAc extract. ^1H NMR ($CDCl_3$): δ 7.32 (d, J = 8.8, 2H); 7.11 (s, 1H); 6.94 (d, J = 8.8, 2H); 4.54 (s, 2H); 3.85 (s, 3H); 3.44 (s, 3H).

[0150] N-(2'-t-Butylaminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methoxymethyl)-1H-pyrazole-5-carboxamide: Oxalyl chloride (460 mg, 3.6 mmol) and dry DMF (2 drops) were added at room temperature to 1-(4-methoxyphenyl)-3-(methoxymethyl)-1H-pyrazole-5-carboxylic acid (236 mg, 0.90 mmol) in dry CH_2Cl_2 (5 mL) and stirred 2 hours under N_2. The resulting solution was evaporated and placed briefly under high vacuum before redissolving in CH_2Cl_2 (2 mL). This solution was added over a few minutes to a mixture of 2'-t-butylaminosulfonyl-4-amino-[1,1']-biphen-4-yl (288 mg, 0.945 mmol) in 5 mL of CH_2Cl_2. The resulting solution was stirred at room temperature under N_2 for 23 hours, diluted with CH_2Cl_2, extracted with H_2O, dried over Na_2SO_4, filtered, and evaporated. The crude product was chromatographed on silica gel (30% EtOAc/hexanes) to yield an white solid (110 mg, 22%). MS (ESI) m/z 571.0 $(M + Na)^+$.

[0151] N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methoxymethyl)-1H-pyrazole-5-carboxamide: N-(2'-t-Butylaminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methoxymethyl)-1H-pyrazole-5-carboxamide (110 mg, 0.20 mmol) was dissolved in 5 mL TFA and stirred at room temperature for 16 hours. The solvent was removed and the product purified by preparative HPLC on a C-18 reversed-phase column (10-90% MeCN/H_2O/0.05% TFA) to yield a white powder (94 mg, 95%). ^1H NMR ($CDCl_3$) : δ 8.15 (d, J = 8.1, 1H); 7.73 (br s, 1H) ; 7.53 (m, 4H); 7.43 (m, 4H) ; 7.32 (d, J = 7.3, 1H); 7.01 (s, 1H); 6.96 (d, J = 9.2, 2H) ; 4.59 (s, 2H); 4.26 (br s, 2H) ; 3.86 (s, 3H) ; 3.49 (s, 3H). HRMS m/z 493.1546 $(M + H)^+$.

EXAMPLE 64

N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-carbomethoxy-1H-pyrazole-5-carboxamide

[0152] 3-formyl-1-(4-Methoxyphenyl)-1H-pyrazole-5-carboxylic acid: Ethyl 3-(dibromomethyl)-1-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate (0.34 g, 0.813 mmol) was dissolved in 2 mL THF and lithium hydroxide (34 mg, 0.816 mmol) was dissolved in 0.5 mL water and added to the methanolic solution. After stirring at room temperature for 16 hours the solvent was evaporated, the residue was dissolved in 10 mL of water, acidified with 1N HCl and extracted with EtOAc to give 66 mg (33%) of the desired product after evaporation. ^1H NMR ($CDCl_3$): δ 10.06 (s, 1H); 7.56 (s, 1H); 7.40 (d, J = 9.1, 2H); 7.01 (d, J = 9.1, 2H); 4.54 (s, 2H); 3.88 (s, 3H).

[0153] N-(2'-t-Butylaminosulfonyl-[1,1']-biphen-4-yl)-3-formyl-1-(4-methoxyphenyl)-1H-pyrazole-5-carboxamide: Oxalyl chloride (20 mL) and dry DMF (2 drops) were added at room temperature to 3-formyl-1-(4-Methoxyphenyl)-1H-pyrazole-5-carboxylic acid (66 mg, 0.25 mmol) in dry CH_2Cl_2 (2 mL) and stirred 2 hours under N_2. The resulting solution was evaporated and placed briefly under high vacuum before redissolving in CH_2Cl_2 (2 mL). This solution was

added over a few minutes to a mixture of 2'-t-butylaminosulfonyl-4-amino-[1,1']biphen-4-yl (51 mg, 0.17 mmol) in 2 mL of CH_2Cl_2. The resulting solution was stirred at room temperature under N_2 for 23 hours, diluted with CH_2Cl_2, extracted with H_2O, dried over Na_2SO_4, filtered, and evaporated. The crude product was chromatographed on silica gel (30% EtOAc/hexanes) to yield an white solid (16.2 mg, 11%). ^1H NMR ($CDCl_3$): δ 10.09 (s, 1H); 8.16 (d, J = 8.1, 1H); 7.77 (br s, 1H); 7.56 (m, 3H); 7.49 (m, 4H); 7.40 (m, 1H); 7.25 (m, 2H); 7.04 (d, J = 8.8, 2H); 3.89 (s, 3H); 3.61 (br s, 1H); 1.02 (s, 9H).

[0154] N-(2'-t-Butylaminosulfonyl-[1,1']-biphen-4-yl)-3-carbomethoxy-1-(4-methoxyphenyl)-1H-pyrazole-5-carboxamide: N-(2'-t-Butylaminosulfonyl-[1,1']-biphen-4-yl)-3-formyl-1-(4-methoxyphenyl)-1H-pyrazole-5-carboxamide (16.2 mg, 0.03 mmol), KCN (6.9 mg, 0.11 mmol), manganese dioxide, activated (100 mg), and acetic acid (1.7 µL, 0.03 mmol) was dissolved/suspended in 1 mL of methanol and stirred at room temperature for 24 hours. The reaction mixture was filtered through Celite and evaporated to 14 mg (82%) of the desired product. ^1H NMR ($CDCl_3$) : δ 8.16 (d, J = 8.1, 1H) ; 7.67 (br s, 1H); 7.53 (m, 3H); 7.48 (m, 4H); 7.27 (m, 2H); 7.02 (d, J = 8.8, 2H); 3.99 (s, 3H); 3.87 (s, 3H); 1.02 (s, 9H).

[0155] N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-3-carbomethoxy-1-(4-methoxyphenyl)-1H-pyrazole-5-carboxamide: N-(2'-t-Butylaminosulfonyl-[1,1']-biphen-4-yl)-3-carbomethoxy-1-(4-methoxyphenyl)-1H-pyrazole-5-carboxamide (14 mg, 0.02 mmol) was dissolved in 2 mL TFA and stirred at room temperature for 16 hours. The solvent was removed and the product purified by preparative HPLC on a C-18 reversed-phase column (10-90% MeCN/H_2O/0.05% TFA) to yield a white powder (9 mg, 81%). ^1H NMR ($CDCl_3$): δ 8.16 (d, J = 8.1, 1H); 7.67 (br s, 1H); 7.50 (m, 11H); 7.31 (d, J = 7.0, 1H); 7.00 (d, J = 8.8, 2H); 4.59 (s, 2H); 4.20 (br s, 2H); 3.99 (s, 3H); 3.87 (s, 3H). HRMS m/z 507.1260 $(M + H)^+$.

EXAMPLE 65

N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylsulfonylmethyl)-1H-pyrazole-5-carboxamide

[0156] Ethyl 1-(4-methoxyphenyl)-3-(methylsulfonylmethyl)-1H-pyrazole-5-carboxylate: Ethyl 3-(bromomethyl)-1-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate (0.4440 g, 1.31 mmol) is dissolved in 10 mL THF with potassium thiomethoxide (0.248 g, 2.88 mmol) and heated to reflux for 14 hours. The reaction mixture was cooled and reduced to 1/10 original volume. The reaction mixture was dissolved in 20 mL of water and extracted with EtOAc and air oxidized over 24 hours to give 0.358 g of a crude mixture. The product was purified by preparative HPLC on a C-18 reversed-phase column (10-90% MeCN/H_2O/0.05% TFA) to yield a white powder 47 mg (11%) of desired product. ^1H NMR ($CDCl_3$): δ 7.32 (d, J = 8.8, 2H); 7.18 (s, 1H); 6.97 (d, J = 8.8, 2H); 4.37 (s, 2H); 4.25 (q, J = 7.1, 2H); 3.86 (s, 3H); 1.28 (t, J = 7.1, 3H).

[0157] N-(2'-t-Butylaminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylsulfonylmethyl)-1H-pyrazole-5-carboxamide: Trimethyl aluminum (0.41 mL, 2.0 M in heptane, 0.83 mmol) was added to 2'-t-butylaminosulfonyl-4-amino-[1,1']biphen-4-yl (50.6 mg, 0.166 mmol) in CH_2Cl_2 (5 mL). After stirring at room temp under N_2 75 minutes, a solution of ethyl 1-(4-methoxyphenyl)-3-(methylsulfonylmethyl)-1H-pyrazole-5-carboxylate (47 mg, 0.139 mmol) in CH_2Cl_2 (2 mL) was added and the resulting solution stirred 70 hours. The reaction was quenched carefully by dropwise addition of 1M HCl, diluted with H_2O, and extracted into CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by preparative HPLC on a C-18 reversed-phase column (10-90% MeCN/H_2O/0.05% TFA) to yield the desired product (80 mg, 100%). ^1H NMR ($CDCl_3$): δ 8.16 (d, J = 8.1, 1H); 7.76 (br s, 1H); 7.49 (m, 8H); 7.27 (m, 1H); 7.08 (m, 1H); 7.01 (d, J = 8.8, 2H); 4.41 (s, 2H); 3.87 (s, 3H); 2.96 (s,3H); 1.02 (s, 9H).

[0158] N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylsulfonylmethyl)-1H-pyrazole-5-carboxamide: N-(2'-t-Butylaminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylsulfonylmethyl)-1H-pyrazole-5-carboxamide (80 mg, 0.15 mmol) was dissolved in 2 mL TFA and stirred at room temperature for 16 hours. The solvent was removed and the product purified by preparative HPLC on a C-18 reversed-phase column (10-90% MeCN/H_2O/0.05% TFA) to yield a white powder (47 mg, 58%). ^1H NMR ($CDCl_3$): δ 8.16 (d, J = 8.1, 1H); 8.06 (br s, 1H); 7.60 (m, 4H); 7.44 (m, 4H); 7.33 (m, 1H); 7.09 (br s, 1H); 7.01 (d, J = 9.1, 2H) ; 4.43 (s, 2H); 4.38 (br s, 2H); 3.87 (s, 3H); 2.97 (s,3H). HRMS m/z 541.1137 $(M + H)^+$.

EXAMPLE 66

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-methanesulfonyl)phenyl)pyrimidin-2-yl) carboxyamide

[0159] 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-methanesulfonyl)phenyl)pyrimidin-

2-yl)carboxyamide: This material was prepared according to the methods described for EXAMPLE 15 with the exception that during the coupling step 2-amino-5-(2-methanesulfonyl)phenyl)pyrimidine was substituted for 4-(2-N-t-butylaminosulfonyl)phenyl)aniline. Purification by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; HRMS $(M+H)^+$ calc. m/z: 518.110986, obs: 518.108715.

EXAMPLE 67

3-methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-2-carbomethoxypyrrolidino)phenyl) carboxyamide

[0160] N-(4-Nitrobenzoyl)-2-carbomethoxypyrrolidine: To 2-carbomethoxypyrrolidine (d,1-proline methylester, 1.64 g, 12.7 mmol) with pyridine (10.1 g, 12.7 mmol) in CH_2Cl_2 (100 mL) at 0°C was added 4-nitrobenzoyl chloride (2.36 g, 12.7 mmol) in CH_2Cl_2 (25 mL) dropwise. The reaction was allowed to warm to ambient temperature and stirred 18 h. The reaction was evaporated and applied to a silica gel flash column and eluted with a gradient of 2:1 Hexane: EtOAc to 1:2 Hexane:EtOAc. There was isolated 1.3 g of the title compound; LRMS $(M+H)^+$ m/z = 279.

[0161] N-(4-Aminobenzoyl)-2-carbomethoxypyrrolidine: N-(4-nitrobenzoyl)-2-carbomethoxypyrrolidine (0.54 g, 1.94 mmol) in MeOH (50 mL) with 10% Pd-C (0.10 g) was shaken under an atmosphere of H_2 gas (50 psi) for 4 h. The reaction was filtered through a plug of Celite® and evaporated to give 0.41 g of the aniline; LRMS $(M+H)^+$ m/z = 249.

[0162] 3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-2-carbomethoxypyrrolidino)phenyl) carboxyamide: This compound was prepared by the methodology described for EXAMPLE 19 with the exception that in the coupling step N-(4-aminobenzoyl)-2-carbomethoxypyrrolidine was used in the place of 2-amino-5-(N-pyrrolidinocarbonyl)pyridine. The solvent was evaporated, the residue dissolved in ethyl acetate and washed with water. After drying and removal of the solvent, the crude product was purified by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; mp 46 °C, HRMS $(M+H)^+$ calc. m/z: 462.190320, obs: 462.188795.

EXAMPLE 68

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-3-aminopyrrolidino)phenyl)carboxyamide

[0163] 3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-3-azidopyrrolidino)phenyl)carboxyamide: To 3-methyl-1-(4-methoxyphenyl)-lH-pyrazole-5-N-(4-(N-carboxyl-3-hydroxypyrrolidino)phenyl)carboxyamide (prepared in EXAMPLE 21, 0.14 g, 0.33 mmol) with Et_3N (0.05 g, 0.5 mmol) in CH_2Cl_2 was added methanesulfonyl chloride (0.057 g, 0.05 mmol). After 18 h the reaction was complete; it was evaporated, dissolved in EtOAc, washed with 1N HCl, dried and evaporated. There was obtained 0.21 g of the methanesulfonate; LRMS $(M-SO_2CH_3)^+$ m/z = 403.

[0164] The methanesulfonate prepared above (0.17 g, 0.35 mmol) and sodium azide (0.11 g, 1.76 mmol) in DMF (10 mL) was heated at 60 °C for 4 h. Brine was added to the cooled reaction mixture and the suspension was extracted with EtOAc (3x). The combined extracts were washed with water (5x), dried (MgS04), and evaporated to give 0.10 g of the azide; LRMS $(M-N_2)^+$ m/z = 418.

[0165] 3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carbaxyl-3-aminopyrrolidino)phenyl)carboxyamide: The azide from above (0.10 g, 0.22 mmol) in MeOH (20 mL) with 10% Pd-C was stirred under an atmosphere of H_2 gas (1 atm). After 2 h the reaction was purged with N_2, filtered through a pad of Celite®, and evaporated. The crude product was purified by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; mp 133.4 °C, HRMS $(M+H)^+$ calc. m/z: 420.203565, obs: 420.203373.

EXAMPLE 69

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-3-methoxypyrrolidino)phenyl)carboxyamide

[0166] 4-(N-carboxyl-3-methoxypyrrolidino)aniline: To 3-hydroxypyrrolidine hydrogen chloride (1.63 g, 14.9 mmol) and triethylamine (1.51 g, 14.9 mmol) in dichloromethane (50 mL) at 0 °C, was added a solution of p-nitrobenzoyl chloride (2.5 g, 12.4 mmol) in dichloromethane (50 mL). The reaction was evaporated to dryness and the residue dissolved in ethyl acetate. This solution was washed with 1N hydrochloric acid solution and brine, then dried and evaporated to give 2.22 g of product; LRMS $(M+H)^+$ m/z: 237.

[0167] To a suspension of NaH (0.16 g of a 60% suspension in mineral oil, 6.89 mmol) in THF (30 mL) was added dropwise a solution of the hydroxy compound prepared above (0.65 g, 2.75 mmol) in THF (10 mL). The reaction was

cooled to 0 °C and methyliodide (0.43 g, 3.03 mmol) was added. The reaction was stirred at ambient temperature for 24 h. The reaction was diluted with Et_2O and washed with 0.5N NH_4Cl, and brine, then dried and evaporated to give the methyl ether (0.47 g); LRMS $(M+H)^+$ m/z = 251.

[0168] The methyl ether (0.42 g, 1.68 mmol) in MeOH (50 mL) with 10% Pd-C (0.05 g) was stirred under an atmosphere of H_2 gas (1 atm) for 3 h. The reaction was purged with N_2, filtered through a Celite® pad and evaporated to give 0.28 g of the aniline; LRMS (M+H)+ m/z = 221.

[0169] 3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-3-methoxypyrrolidino)phenyl)carboxyamide: This compound was prepared by the methodology described for EXAMPLE 19 with the exception that in the coupling step 4-(N-carboxyl-3-methoxypyrrolidino)aniline was used in the place of 2-amino-5-(N-pyrrolidinocarbonyl)pyridine. The solvent was evaporated, the residue dissolved in ethyl acetate and washed with water. After drying and removal of the solvent, the crude product was purified by HPLC utilizing gradient elution with a mixture of water: acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; mp 40.2 °C, HRMS $(M+H)^+$ calc. m/z: 434.195406, obs: 434.194469.

EXAMPLE 70

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-aminosulfonyl)phenyl)pyridin-2-yl) carboxyamide

[0170] 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-aminosulfonyl)phenyl)pyridin-2-yl)carboxyamide: This material was prepared according to the methods described for EXAMPLE 15 with the exception that during the coupling step 2-amino-5-(2-N-t-butylaminosulfonyl)phenyl)pyridine was substituted for 4-(2-N-t-butylaminosulfonyl)phenyl)aniline. The t-butylsulfonamide group was removed by heating the coupling product at reflux in TFA for 1 h, then removing the TFA by distillation in vacuo. Purification of the final product was by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; HRMS $(M+H)^+$ calc. m/z: 518.110986, obs: 518.112930.

EXAMPLE 71

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-amidino)phenyl)carboxyamide • TFA

[0171] 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-cyano)phenyl)carboxyamide: To 3-trifluoromethyl-5-methyl-1-(4-methoxyphenyl)-1H-pyrazole (EXAMPLE 15, 0.6 g, 2.1 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added oxalyl chloride in CH_2Cl_2 (2M solution, 1.6 mL, 3.15 mmol) followed by a few drops of DMF. The reaction was allowed to warm to ambient temperature and stirred 18 h. The reaction was evaporated and pumped on for several hours to remove the last traces of HCl. The acid chloride was combined with p-aminobenzonitrile (0.3 g, 2.52 mmol) and DMAP (0.77 g, 6.3 mmol) in CH_2Cl_2 (40 mL) and stirred at ambient temperature for 18 h. The reaction was evaporated and then partioned between 1N HCl and EtOAc. The EtOAc layer was dried and evaporated to give 0.79 g of crude product. Further purification was effected by MPLC with a column of 200 g of flash silica, eluting with 3:1 Hexane: EtOAc and collecting 25 mL fractions. The 0.45 g of the desired nitrile was obtained from fractions 30-65; mp 188.2, HRMS $(M+H)^+$ calc. m/z: 386.099081, obs: 386.098101.

[0172] 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(O-methyl)formimino)phenyl)carboxyamide •HCl: A stream of anhydrous HCl gas was passed through a solution of 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-cyano)phenyl)carboxyamide (225 mg, 0.58 mmol) in dry MeOAc (25 mL) and dry MeOH (5 mL) at 0°C until saturation. After standing for 18 h at 10°C, the tightly stoppered flask was unsealed and the solvent was removed by distillation *in vacuo*. The residue was repeatedly evaporated with dry Et_2O, then pumped on for several hours to remove the last traces of HCl.

[0173] 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-amidino)phenyl)carboxyamide • TFA: The imidate (0.58 mmol) prepared above was dissolved in dry MeOH (10 mL) and $(NH_4)_2CO_3$ (0.32 g, 3.33 mmol) was added. This mixture was stirred at ambient temperature for 18 h, then evaporated to dryness. Purification of the final product was by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; mp 232.5, HRMS $(M+H)^+$ calc. m/z: 404.133435, obs: 404.132331.

EXAMPLE 72

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-byrazole-5-(N-(4-(N-pyrrolidino)formylimino)phenyl)carboxyamide • TFA

[0174] 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-pyrrolidino)formylimino)phenyl)carboxyamide • TFA: 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(O-methyl)formimino)phenyl)carboxyamide·HCl (EXAMPLE 71, 0.58 mmol) prepared above was dissolved in dry MeOH (10 mL) and pyrrolidine (0.12 g, 1.74 mmol) was added. This mixture was stirred at ambient temperature for 18 h, then evaporated to dryness. Purification of the final product was by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; mp 89.5, HRMS $(M+H)^+$ calc. m/z: 458.180385, obs: 458.183032.

EXAMPLE 73

3-Trifluoromethyl-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))-1-(4-methoxyphenyl)pyrrolo[3,4-d]pyrazole-4,6-(1H, 5H)-dione

[0175] 1,1,1-Trifluoroacetaldehyde-N-(4-methoxyphenyl)hydrazone: A mixture of 1,1,1-trifluoroacetaldhyde ethyl hemiacetal (4.2 g, 34.17 mmol) and 4-methoxyphenylhydrazine • HCl (4.97 g, 28.48 mmol) in EtOH (100 mL) was brought to reflux, then cooled to ambient temperature when all of the components were dissolved. The reaction was evaporated to dryness to give 5.34 g of a black oil that was used in the next step without further purification; LRMS $(M+H)^+$ m/z = 219.2.

[0176] 1,1,1-Trifluoroacetoyl bromide-N-(4-methoxyphenyl)hydrazone: To the black oil (0.87 g, 4 mmol) produced above in DMF (25 mL) at 0 °C was added N-bromosuccinimide (0.72 g, 4 mmol) portionwise. The reaction was complete in 2 h (TLC, 3:1 Hexane:EtOAc). The reaction was diluted with brine and extracted with EtOAc. The extracts were washed with brine (5x), dried ($MgSO_4$) and evaporated to give 0.69 g of product as a black oil. This material was used without further purification.

[0177] 4- (2-N-*t*-Butylaminosulfonyl)phenyl)bromomaleimide: Bromomaleic anhydride (0.29 g, 1.65 mmol) was added to 4-(2-N-t-butylaminosulfonyl)phenyl)aniline (0.5 g, 1.65 mmol) in THF (10 mL). After 1 h the solution was cooled to 0 °C and N-methylmorpholine (0.2 g, 1.98 mmol) followed by isobutylchloroformate (0.27 g, 1.98 mmol) was added. The reaction was allowed to warm to ambient temperature and stirred 18 h. The reaction was evaporated, dissolved in EtOAc, washed with 1N HCl, dried and evaporated. The product was purified further by MPLC using a column of 200 g of flash silica and eluting with 3:1 hexane:EtOAc and 25 mL fractions collected. The desired product (0.39 g) was isolated from fractions 35-65;HRMS $(M+H)^+$ calc. m/z: 462.024890, obs: 462.025783.

[0178] 3-Trifluoromethyl-5-(N-(2'-N-t-butylaminosulfonyl-[1,1']-biphen-4-yl))-1-(4-methoxyphenyl)pyrrolo [3,4-d]pyrazole-4,6-(1H, 5H)-dione: A mixture of 1,1,1-trifluoroacetoyl bromide-N-(4-methoxyphenyl)hydrazone (0.68 g, 2.29 mmol) and 4-(2-N-t-butylaminosulfonyl)phenyl)bromomaleimide (0.2 g, 0.4 mmol) with Et_3N (0.35 g, 3.45 mmol) in toluene were heated at reflux for 3 h. The reaction was diluted with EtOAc, washed with 1N HCl, dried ($MgSO_4$) and evaporated to give 0.35 g of crude product. The product was isolated using MPLC by eluting the crude material from a column of flash silica gel (200 g) with 3:1 hexane:EtOAc and collecting 25 mL fractions. Fractions 33-58 yielded 0.15 g of pure material; mp 196.1 °C, HRMS $(M+H)^+$ calc. m/z: 653. 165176, obs: 653.166000.

[0179] 3-Trifluoromethyl-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))-1-(4-methoxyphenyl)pyrrolo[3,4-d]pyrazole-4,6-(1H, 5H)-dione: The product from above (0.15 g, 0.25 mmol) was heated at reflux in TFA for 1 h. The reaction was cooled and evaporated to give 0.14 g of crude material. The product was isolated using MPLC by eluting the crude material from a column of flash silica gel (200 g) with 2:1 hexane:EtOAc and collecting 25 mL fractions. Fractions 55-90 were combined and triturated with a small quantity of Et_2O. This process gave 0.06 g of pure material; mp 210.7 °C, HRMS $(M+H)^+$ calc. m/z: 543.095002, obs: 543.097942.

EXAMPLE 74

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-carbomethoxy-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)) carboxyamide

AND EXAMPLE 75

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-hydoxymethyl-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)) carboxyamide

[0180] Preparation of a mixture of 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-carbomethoxy-(N-(2'-N-t-butylaminosulfonyl-[1,1']-biphen-4-yl))carboxyamide and 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-hydoxymethyl-(N-(2'-N-t-butylaminosulfonyl-[1,1']-biphen-4-yl))carboxyamide: 3-Trifluoromethyl-5-(N-(2'-N-t-butylaminosulfonyl-[1,1']-biphen-4-yl))-1-(4-methoxyphenyl)pyrrolo[3, 4-d]pyrazole-4,6-(1H, 5H)-dione (0.37 g, 0.62 mmol) in AcCN (30 mL) was added dropwise to a solution of NaBH4 (0.096 g, 2.48 mmol) in MeOH (20 mL) at 0 °C. The reaction was complete in less than 1 h (TLC, 3:1 hexane:EtOAc). It was evaporated, dissolved in EtOAc and washed with 1N HCl. The organic layer was dried and evaporated to give a mixture of the title compounds (0.37 g). This mixture was separated by MPLC using a 400 g column of flash silica gel and eluting with 2:1 hexane: EtOAc; 25 mL fractions of eluent were collected.

[0181] From fractions 50-66, 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-carbomethoxy-(N-(2'-N-t-butylaminosulfonyl-[1,1']-biphen-4-yl))carboxyamide (0.15 g) was isolated; HRMS $(M+Na)^+$ calc. m/z: 653.165761, obs: 653.164400.

[0182] From fractions 69-100, 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-hydoxymethyl-(N-(2'-N-t-butylaminosulfonyl-[1,1']-biphen-4-yl))carboxyamide (0.12 g) was isolated; HRMS $(M+Na)^+$ calc. m/z: 625.170847, obs: 625.169900.

[0183] 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-carbomethoxy-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxyamide: The product from fractions 50-66 (0.15 g) was heated at reflux in TFA for 1 h. The reaction was cooled and evaporated to give 0.14 g of crude material. Purification of the final product was by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of Example 74; mp 233.3 °C, HRMS $(M+H)^+$ calc. m/z: 575.121216, obs: 575.120500.

[0184] 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-hydroxymethyl-(N-(2 aminosulfonyl-[1,1']-biphen-4-yl))carboxyamide: The product from fractions 69-100 (0.12 g) was heated at reflux in TFA for 1 h. The reaction was cooled and evaporated to give 0.11 g of crude material. Purification of the final product was by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of Example 75; mp 115.4 °C, HRMS $(M+H)^+$ calc. m/z: 547.126302, obs: 547.124400.

EXAMPLE 7 6

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-2-fluoro(4-(N-pyrrolidino)formylimino)phenyl) carboxyamide • TFA

[0185] 3-Fluoro-4-nitrobenzamide: 3-Fluoro-4-nitrobenzoic acid (5.0 g, 27 mmol) and $SOCl_2$ (6.42 g, 54 mmol) with a few drops of DMF in benzene (100 mL) was heated at reflux for 3 h. The reaction was evaporated to dryness, then evaporated several times with Et_2O to purify, yield 5.56 g.

[0186] The acid chloride prepared above was dissolved in EtOAc (50 mL) and added dropwise to a 0 °C biphasic mixture of EtOAc (150 mL) and conc. NH_4OH (100 mL). After 30 min, the layers were separated, the water layer saturated with NaCl and extracted with EtOAc. The combined organic extracts were dried and evaporated to give a 4.85 g of the benzamide; LRMS/ES$^-$ $(M-H)^-$ m/z = 182.9.

[0187] 3-Fluoro-4-aminobenzonitrile: To a 0 °C EtOAc (150 mL) solution of 3-fluoro-4-nitrobenzamide (4 85 g, 26.4 mmol) and Et_3N (5.34 g, 52.8 mmol) was added dropwise a CH_2Cl_2 (50 mL) solution of 1,1,1-trichloroacetyl chloride (5.28 g, 29.04 mmol). The reaction was complete in 2 h (TLC, 1:1 hexane:EtOAc), then it was washed with 1N HCl, dried ($MgSO_4$) and evaporated to give 4.1 g of the corresponding nitrile.

[0188] The 4-nitrobenzonitrile derivative prepared above (4.1 g, 24.7 mmol) in EtOH/water (80 mL/40 mL) was heated at reflux with iron powder (8.3 g, 148 mmol) and NH_4Cl (0.83 g, 15.3 mmol) for 2 h. The reaction was filtered and evaporated to dryness. The residue was dissolved in EtOAc, washed with brine and dried (MgSO4) to give 2.68 g of product; LRMS $(M+H)^+$ m/z = 137.0. The product was purified further by MPLC on a 360 g column of flash silica gel and eluting with 3:1 hexane:EtOAc ; 25 mL fractions were collected. From fractions 128-195, 1.32 g of pure product was obtained.

[0189] **3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-cyano)phenyl)carboxyamide:** To 3-trifluoromethyl-5-methyl-1-(4-methoxyphenyl)-1H-pyrazole (EXAMPLE 15, 1.13 g, 3.95 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added oxalyl chloride in CH_2Cl_2 (2M solution, 2.96 mL, 5.93 mmol) followed by a few drops of DMF. The reaction was allowed to warm to ambient temperature and stirred 18 h. The reaction was evaporated and pumped on for several hours to remove the last traces of HCl.

[0190] The acid chloride was combined with 3-fluoro-4-aminobenzonitrile (0.59 g, 4.35 mmol) and DMAP (1.45 g, 11.85 mmol) in CH_2Cl_2 (100 mL) and stirred at ambient temperature for 18 h. The reaction was evaporated then partitioned between 1N HCl and EtOAc. The EtOAc layer was dried and evaporated to give 0.79 g of crude product. Further purification was effected by MPLC with a column of 360 g of flash silica, eluting with 4: 1 Hexane:EtOAc and collecting 25 mL fractions. The 0.83 g of the desired nitrile was obtained from fractions 91-133; mp 160.6, LRMS $(M+H)^+$ m/z = 405.0.

[0191] **3-Trifluoromnethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-(O-methyl)formimino)phenyl) carboxyamide •HCl: A** stream of anhydrous HCl gas was passed through a solution of 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-cyano)phenyl)carboxyamide (0.83 g, 2.05 mmol) in dry MeOAc (50 mL) and dry MeOH (10 mL) at 0 °C until saturation. After standing for 18 h at 10 °C, the tightly stoppered flask was unsealed and the solvent was removed by distillation *in vacuo*. The residue was then repeatedly evaporated with dry Et_2O, then pumped on for several hours to remove the last traces of HCl.

[0192] **3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-(N-pyrrolidino)formylimino)phenyl)carboxyamide • TFA:** 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-(O-methyl)formimino) phenyl)carboxyamide •HCl (2.05 mmol) prepared above was dissolved in dry MeOH (15 mL) and pyrrolidine (0.44 g, 6.15 mmol) was added. This mixture was stirred at ambient temperature for 18 h, then evaporated to dryness. Purification of the final product was by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; mp 61.8 °C, HRMS $(M+H)^+$ calc. m/z: 476.170963, obs: 476.170693.

EXAMPLE 77

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-pyrrolidino)formyl-N-((2-propyl) methylcarbamoyl)imino)phenyl)carboxyamide

[0193] **3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-pyrrolidino)formyl-N-((2- propyl)methylcarbamoyl)imino)phenyl)carboxyamide:** To 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-pyrrolidino)formylimino)phenyl)carboxyamide • TFA (EXAMPLE 72, (0.311 g) was added 1N NaOH (25 mL), a suspension formed which was extracted with CH_2Cl_2 (2x35 mL). The organic extracts were dried and evaporated to give 0.18 g (0.39 mmol) of the free base. The free base was re-dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C, then Et_3N (0.08 g, 0.78 mmol) was added. To the cooled solution 4.4 mL (0.44 mmol) of a 0.1N solution of isobutylchloroformate (from 0.01 mol [1.3 mL] of neat isobutylchloroformate in 100 mL of CH_2Cl_2) was added dropwise and stirred at 0 °C for 2 h. The reaction was evaporated and partitioned between EtOAc and 1N HCl. The EtOAc layer was dried and evaporated to give 0.10 g of crude material. This was purified further by MPLC using a 200 g column of flash silica gel and eluting with 2:1 hexane:EtOAc. 25 mL fractions were collected and 0.056 g of pure product was isolated from fractions 40-80; mp 90.1 °C, HRMS $(M+H)^+$ calc. m/z: 558.2345, obs: 558.2334.

EXAMPLE 78

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-pyrrolidino)formyl-N-(methanesulfamoyl) imino)phenyl)carboxyamide

[0194] **3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-pyrrolidino)formyl-N-(methanesulfamoyl)imino)phenyl)carboxyamide:** To 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-pyrrolidino) formylimino)phenyl)carboxyamide • TFA (EXAMPLE 72, (0.332 g) was added 1N NaOH (25 mL), a suspension formed which was extracted with CH_2Cl_2 (2x35 mL). The organic extracts were dried and evaporated to give 0.18 g (0.39 mmol) of the free base. The free base was re-dissolved in CH_2Cl_2 (25 mL) and cooled to 0 °C, then DMAP (0.095 g, 0.78 mmol) was added. To the cooled solution 4.2 mL (0.42 mmol) of a 0.1N solution of methanesulfonyl chloride (from 0.01 mol [0.78 mL] of neat methanesulfonyl chloride in 100 mL of CH_2Cl_2) was added dropwise and stirred at 0 °C for 48 h. The reaction was evaporated and partitioned between EtOAc and 1N HCl. The EtOAc layer was dried and evaporated to give 0.11 g of crude material. This was purified further by MPLC using a 200 g column of flash silica gel and eluting with 2:1 hexane:EtOAc. 25 mL fractions were collected and 0.050 g of pure product was isolated from fractions 81-130; mp 117.2 °C, HRMS $(M+Na)^+$ obs. m/z: 558.1381.

EXAMPLE 79

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((4-amidino)phenyl)methyl)carboxyamide • TFA

[0195] **α-Amino-4-cyanotoluene:** A mixture of 4-cyanobenzyl bromide (3 g, 15.3 mmol) and NaN_3 (1.99 g, 30.6 mmol) in DMF (20 mL) was stirred at ambient temperture for 18 h. The reaction was diluted with brine and extracted with EtOAc. The organic extracts were washed with brine (5x), dried ($MgSO_4$) and evaporated to give 1.87 g of the benzylic azide product.

[0196] The benzylic azide (1.87 g, 11.84 mmol) and $SnCl_2 \cdot H_2O$ (7.25 g, 32.2 mmol) in MeOH (50 mL) was stirred at ambient temperature for 18 h. The solution was evaporated to dryness then the residue was dissolved in 1N NaOH and extracted with EtOAc. The EtOAc layer was washed with brine, dried and evaporated to give 0.83 g of α-amino-4-cyanotoluene.

[0197] **3-Trifluoromethyl-1-(4-methoxyphenyl)-1N-pyrazole-5-(N-((4-cyano)phenyl)methyl)carboxyamide:** To 3-trifluoromethyl-5-methyl-1-(4-methoxyphenyl)-1H-pyrazole (EXAMPLE 15, 0.4 g, 1.4 mmol) and N-methylmorpholine (0.156 g, 1.54 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added isobutylchloroformate (0.21 g, 1.54 mmol). The reaction was stirred for 30 min at 0 °C and 0.203 g of α-amino-4-cyanotoluene (1.54 mmol) in CH_2Cl_2 (8 mL) was added. After 18 h the reaction was washed with 1N HCl and 1N NaOH, then dried and evaporated to give 0.54 g of crude material. Further purification was effected by MPLC with a column of 200 g of flash silica, eluting with 2:1 Hexane:EtOAc and collecting 25 mL fractions. The 0.32 g of the desired nitrile was obtained from fractions 61-120; mp 197.5, LRMS $(M+H)^+$ m/z = 401.0.

[0198] **3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((2-fluoro-4-(O-methyl)formimino)phenyl) methyl)carboxyamide •HCl:** A stream of anhydrous HCl gas was passed through a solution of 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((4-cyano)phenyl)methyl)carboxyamide (0.32 g, 0.8 mmol) in dry MeOAc (25 mL) and dry MeOH (5 mL) at 0 °C until saturation. After standing for 18 h at 10 °C, the tightly stoppered flask was unsealed and the solvent was removed by distillation in vacuo. The residue was then repeatedly evaporated with dry Et_2O, then pumped on for several hours to remove the last traces of HCl.

[0199] **3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((4-amidino)phenyl)methyl)carboxyamide • TFA:** The imidate (0.4 mmol) prepared above was dissolved in dry MeOH (15 mL) and $(NH_4)_2CO_3$ (0.192 g, 2.0 mmol) was added. This mixture was stirred at ambient temperature for 18 h, then evaporated to dryness. Purification of the final product was by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; mp 131.4, HRMS $(M+H)^+$ obs. m/z: 418.1478.

EXAMPLE 80

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((4-(N-pyrrolidino)formylimino)phenyl)methyl) carboxyamide • TFA

[0200] **3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((4-(N-pyrrolidino)formylimino)phenyl)methyl)carboxyamide • TFA:** 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((4-(O-methyl)formimino)phenyl) methyl)carboxyamide •HCl (EXAMPLE 79, 0.4 mmol) prepared above was dissolved in dry MeOH (15 mL) and pyrrolidine (0.09 g, 1.2 mmol) was added. This mixture was stirred at ambient temperature for 18 h, then evaporated to dryness. Purification of the final product was by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; LRMS $(M+H)^+$ m/z: 472.3.

EXAMPLE 81

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((1-benzyl)piperidin-4-yl)carboxyamide • TFA

[0201] **3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((1-benzyl)piperidin-4-yl)carboxyamide • TFA:** To 3-trifluoromethyl-5-methyl-1-(4-methoxyphenyl)-1H-pyrazole (EXAMPLE 15, 2.86 g, 10 mmol) and N-methyl morpholine (1.01 g, 10 mmol) in THF (50 mL) at 0 °C was added isobutylchloroformate (1.36 g, 10 mmol). The reaction was stirred for 30 min at 0 °C and 1.90 g of 1-benzyl-4-aminopiperidine (10 mmol) was added. After 18 h the reaction was evaporated to dryness and dissolved in 1N NaOH, then extracted with EtOAc. The EtOAc layer was washed with brine, then dried and evaporated to give 4.36 g of crude material. Recrystallization with n-butylchloride gave 1.16 g of product; mp 120.8 °C.

[0202] A 0.10 g sample was dissolved in Et_2O and TFA added to form the TFA salt. Trituration with Et_2O and n-

butylchloride gave 0.015 g of pure product; mp 175.6 °C, HRMS $(M+H)^+$ calc. m/z: 459.200, obs: 459.199.

EXAMPLE 82

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((1-(pyridin-2-yl)methyl)piperidin-4-yl)carboxyamide • TFA

[0203] 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(piperidin-4-yl)carboxyamide • HCl: To a solution of 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((benzyl)piperidin-4-yl)carboxyamide (EXAMPLE 81, 1.06 g, 2.31 mmol) in CH_2Cl_2 (40 mL) was added 1-chloroethylchloroformate (0.5 g, 3.5 mmol). The reaction was stirred for 2 h, then evaporated to dryness. The residue was dissolved in MeOH (50 mL) and heated at reflux for 1 h. The reaction was evaporated to give 0.8 g of product; LRMS $(M+H)^+$ m/z: 369.2.

[0204] 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((1-(pyridin-2-yl)methyl)piperidin-4-yl)carboxyamide • TFA: To 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(piperidin-4-yl)carboxyamide • HCl (0.21 g) and K_2CO_3 (0.3 g) in AcOH (20 mL) was added 2-picolyl chloride (0.16 g). The reaction was stirred at ambient temperature for 18 h. The reaction was diluted with water and extracted with EtOAc (3x). The extracts were dried ($MgSO_4$) and evaporated to give 0.29 g of crude product. Purification of the final product was by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; LRMS $(M+H)^+$ m/z: 460.3.

EXAMPLE 83

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(2-methylimidazo-1-yl))phenyl)carboxyamide • TFA

[0205] 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(2-methylimidazo-1-yl))phenyl)carboxyamide • TFA: A mixture of 3-trifluoromethyl-5-methyl-1-(4-methoxyphenyl)-1H-pyrazole (EXAMPLE 15, 0.20 g, 0.7 mmol), BOP (0.44 g, 1 mmol), Et_3N (0.1 g, 1 mmol) and 1-(4-aminophenyl)-2-methylimidazole (0.17 g, 1 mmol) in DMF (20 mL) was heated at 50-55 °C for 1 h, then cooled to ambient temperature and stirred 18 h. The reaction was diluted with water and extracted with EtOAc. The EtOAc extracts were washed with water (5x), dried ($MgSO_4$) and evaporated. Purification of the final product was by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave a pure sample of the title compound; mp 103.7 °C, HRMS $(M+H)^+$ m/z: 442.188.

EXAMPLE 84

3-Methyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-(4-(5-methylimidazol-1-yl}phenyl)carboxyamide

and EXAMPLE 85

3-Methyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(4-methylimidazol-1-yl}phenyl)carboxyamide.

[0206] N-(4-nitrophenyl)-5-methylimidazole: A solution of p-nitrofluorobenzene (2 g, 14 mmol) in DMF (20 mL) was treated with potassium carbonate (8 g, 58 mmol) and 4-methylimidazole (1.2 g, 14.mmol). After refluxing for 18 h, the reaction mixture was cooled down and concentrated at reduced pressure. The residue was treated with water and the mixture was extracted with ethyl acetate and dried over magnesium sulphate. The organic layer was concentrated and the residue was purified by flash-chromatography (methanol/methylene chloride, 0.5:9.5) affording 1.8 g (62%) of p-nitro-4 (5)-methyl-imidazol-1-yl as 7:1 mixture of regioisomers.

[0207] N-(4-aminophenyl)-5-methylimidazole: Reduction in MeOH:TFA(9.5:0.5) with 0.1 eq. of Pd/C (10%) at 55 psi at ambient temperature over 20 h, followed by filtration over Celite afforded 1.4 g (93%)of p-amino-4 (5)-methyl-imidazol-1-yl.

[0208] Preparation of the mixture of 3-methyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-(4-(5-methyl-imidazol-1-yl)phenyl)carboxyamide and 3-methyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(4-methylimidazol-1-yl}phenyl)carboxyamide: A solution of 3-methyl-1-(4-methoxyphenyl)-1H-pyrazolecarboxylic acid (200 mg, 0.8 mmol) in acetonitrile (5 mL) was treated with an excess of thionyl chloride. The resultant mixture was refluxed for 2h, cooled down, concentrated, dissolved in methylene chloride (5 mL) and treated with DMAP (0.22 mg, 1.8 mmol) and N-(4-aminophenyl)-5-methylimidazole (131 mg, 0.7 mmol). The reaction mixture was stirred at ambient temperature for 18h. The residue was treated with water and the mixture was extracted with ethyl acetate and dried over magnesium sul-

phate. The organic layer was concentrated and the residue was purified by flash-chromatography (methanol/methylene chloride, 0.5:9.5) affording a mixture of 3-methyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(5-methyl-imidazol-1-yl}phenyl)carboxyamide and 3-methyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(4-methyl-imidazol-1-yl}phenyl)carboxyamide. The final products were purified by normal phase HPLC eluting with solvent A (hexane) and solvent B(ethanol) using 80% of A and 20% of B and eluting at 7.5 mL/min.

[0209] EXAMPLE 84: 3-methyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(5-methyl-imidazol-1-yl}phenyl) carboxyamida: ^{1}H NMR ($CDCl_3$): 2.19 (s, 3H), 2.38 (s, 3H), 3.85 (s, 3H), 6.76 (s, 1H), 6.97 (m, 2H), 7.14 (m, 1H), 7.25 (m, 2H), 7.39 (m, 2H), 7.50 (s, 1H), 7.71 (m, 2H), 8.05 (s, 1H).

[0210] EXAMPLE 85: 3-methyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(4-methyl-imidazol-1-yl}phenyl) carboxyamide: ^{1}H NMR ($CDCl_3$): 2.31 (s, 3H), 2.36 (s, 3H), 3.83 (s, 3H), 6.71 (s, 1H), 6.94 (m, 3H), 7.26 (m, 2H), 7.39 (m, 2H), 7.58 (m, 2H), 7.92 (s, 1H), 8.23 (s, 1H).

EXAMPLE 86

3-Trifluoromethyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(5-carbomethoxy-imidazol-1-yl}phenyl) carboxyamide

[0211] Butyl glyoxyl(4-nitroanilino)imine: A solution of p-nitroaniline (6.3 g, 53.4 mmol) in ethyl alcohol (50 mL) was treated with n-butyl gluoxylate (8 g, 53.8 mmol). After stirring at ambient temperature for 18h, the reaction mixture was concentrated at reduced pressure. The residue was treated with water and the mixture was extracted with ethyl acetate and dried over magnesium sulphate. The organic layer was concentrated to afford the title compound in nearly quantitative yield, which was used without further purification. **4-Amino-(5-(carbomethoxy)imidazol-1-yl)benzene:** To the solution of butyl glyoxyl(4-nitroanilino)imine (1.6 g, 6.9 mmol) in methyl alcohol (10 mL) was added potassium carbonate (1.9 g, 13.9 mmol) and tosylmethyl isocyanate (2.3 g, 11.8 mmol). The solution was stirred for 1h at rt, then solvent was removed under reduced pressure. The residue was treated with the saturated sodium chloride solution and the mixture was extracted with methylene chloride. The organic extract was concentrated and triturated with methyl alcohol. The precipitate was collected and dried to afford an intermediate 4-nitro-(5-(carbomethoxy)imidazol-1-yl)benzene (1.5 g, 94%). MS (ES) m/z (rel. intensity), 249 (M+, 100).

[0212] Reduction to 4-amino-(5-(carbomethoxy)imidazol-1-yl)benzene was accomplished according to the procedure described in EXAMPLES 84 and 85; MS (ES) m/z (rel. intensity), 219 (M+, 100).

[0213] 3-Trifluoromethyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(5-carbomethoxy-imidazol-1-yl}phenyl)carboxyamide: A solution of 4-amino-(5-(carbomethoxy)imidazol-1-yl)benzene (152 mg, 0.7 mmol) was coupled with 3-trifluoromethyl-(4-methoxy)phenyl-1H-pyrazole-5-carbonyl chloride (205 mg, 0.7 mmol) according to the procedure, described in EXAMPLES 84 and 85. Purification by flash chromatography (methanol/methylene chloride, 1:9) afforded 3-trifluoromethyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(5-carbomethoxy-imidazol-1-yl}phenyl)carboxyamide, (70 mg, 20%); MS (ES) m/z (rel. intensity), 486 (M+, 100).

EXAMPLE 87

3-Trifluoramethyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(5-carboxy-imidazol-1-yl}phenyl)carboxyamide

[0214] 3-Trifluoromethyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(5-carboxy-imidazol-1-yl}phenyl)carboxyamide: 3-Trifluoromethyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(5-carbomethoxyimidazol-1-yl}phenyl)carboxyamide (147 mg, 0.3 mmol) was suspended in 4:1 mixture of THF and water and treated with LiOH (37 mg, 0.9 mmol) in 0.5 mL of water. The reaction mixture was allowed to stir for 1 hr at ambient temperature, neutralized with 1N HCl, extracted with ethyl acetate, dried over $MgSO_4$ and concentrated to give the acid. The final product was purified by reverse phase HPLC on a Vydec® C-18 column eluting with solvent mixture A (water:TFA, 99.5:0.5) and solvent mixture B (acetonitrile:water:TFA, 90:9.5:0.5) using a gradient starting with A at 100% and changing to B at 100% over 60 min ; MS (ES) m/z (rel. intensity), 471.9 (M+, 100).

EXAMPLES 88-90

[0215] The crude acid, 3-trifluoromethyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(5-carboxy-imidazol-1-yl}phenyl) carboxyamide, was dissolved in acetonitrile, treated with excess thionyl chloride and refluxed over a period of 2hr. The solvent was removed under reduced pressure. The coupling with the amines specified below was conducted according to the procedure described in EXAMPLES 84 and 85 to afford EXAMPLES 88-90. The final products were purified by reverse phase HPLC on a Vydec® C-18 column eluting with solvent mixture A (water:TFA, 99.5:0.5) and solvent mixture B (acetonitrile:water:TFA, 90:9.5:0.5) using a gradient starting with A at 100% and changing to B at 100% over 60 min

to obtain EXAMPLES 88-90 as the trifluoroacetic acid salts.

[0216] EXAMPLE 88: 3-Trifluoromethyl-(4-mothoxy)phenyl-1H-pyrazole-5-(N-{4-(5-N-methylcarbamide-imidazol-1-yl}phenyl)carboxyamide: Prepared using an excess of N-methylamine•HCl; 1H NMR ($CDCl_3$): 2.89 (d, J = 4.7 Hz, 3H), 6.13 (m, 1H), 6.98 (d, J = 9.1 Hz, 3H), 7.15 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.48 (m, 3H), 7.59 (s, 1H), 8.79 (s, 1H).

[0217] EXAMPLE 89: 3-Trifluoromethyl-(4-methoxy)phonyl-1H-pyrazole-5-(N-{4-(5-carbamide-imidazol-1-yl} phenyl)carboxyamide: Prepared by saturating the 0 °C CH_2Cl_2 solution of the acid chloride with NH_3 gas; MS (ES) m/z (rel. intensity), 468.9 (M+, 100)

[0218] EXAMPLE 90: 3-Trifluoromethyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(5-methylsulfonylcarbamide-1-imidazole}phenyl)carboxyamide: Prepared using methane sulfonamide as the amine component; MS (ES) m/z (rel. intensity), 546.9 (M+, 100)

EXAMPLE 91

1-(4'-Methoxyphenyl)-3-hydroxylmethyl-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phenyl)carboxyamide

[0219] 1-(4'-methoxyphenyl)-3-hydroxylmethyl-1H-pyrazole-5-ethylcarboxylate: To a solution of 1-(4'-methoxyphenyl)-3-methyl-1H-pyrazole-5-ethylcarboxylate (1.58 g, 7.1 mmol) in CCl_4 (250 mL) was added NBS (1.5 g, 8.5 mmol) and benzoyl peroxide (73 mg, 4 mmol%). The mixture was degassed and filled with nitrogen, refluxed for 18 hours under nitrogen, and then cooled to room temperature. The mixture was diluted with CH_2Cl_2 (100 mL), washed with 10% NaOH (20 mLx3), water (20 mLx3), and brine (10 mLx2), and dried over $MgSO_4$. Filtration and concentration gave crude 1-(4'-methoxyphenyl)-3-bromomethyl-1H-pyrazole-5-ethylcarboxylate (2.4 g). To a solution of the crude in aqueous DMSO (75%, 40 mL) was added Cu_2O (1.5 g, 10.5 mmol), and the mixture was stirred at 60 °C for 2 hours. The mixture was filtered to remove excess Cu_2O, and the filtrate was extracted with ethyl ether. The ether layer was washed with brine (10 mLx5) and dried over $MgSO_4$. Filtration and concentration, followed by purification by silica gel column chromatography with EtOAc/CH_2Cl_2 (1 to 1) gave the title compound (1.5 g, 81% yield). ESMS $(M+H)^+$ m/z: 277.

[0220] 1-(4'-Methoxyphenyl)-3-hydroxylmethyl-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phenyl)carboxyamide: To a solution of 4-(pyrrolidinyl-one)aniline (390 mg, 2.05 mmol) in CH_2Cl_2 (20 mL) was added $AlMe_3$ (2M in hexane, 3 mmol) at 0°C. The mixture was stirred at room temperature for 15 minutes and a solution of 1-(4'-methoxyphenyl)-3-hydroxylmethylene-1H-pyrazole-5-ethylcarboxylate (560 mg, 2.05 mmol) in CH_2Cl_2 (5 mL) was added. The resulting mixture was stirred overnight, quenched with water (5 mL), and filtered through a pad of Celite to remove Al $(OH)_3$. The filtrate was washed with water and brine, and dried over $MgSO_4$. Filtration, concentration, and purification by silica gel column chromatography with gradient solvents (CH_2Cl_2 to EtOAc) gave the title compound (570 mg, 67% yield). ESMS $(M+Na)^+$ m/z: 443. HRMS (M+H)+ calc. m/z: 420.1798, obs: 420.1771.

EXAMPLE 92

1-(4'-Methoxyphenyl)-3-formaldehyde-1H-pyrazole-5-N-(4'-(pyrrolidinocarbonyl)phenyl)carboxyamide

[0221] To a solution of 1-(4-methoxyphenyl)-3-hydraxylmethyl-1H-pyrazole-5-N-((4'-pyrrolidinocarbonyl)phenyl)carboxyamide 6 (140 mg, 0.33 mmol) in THF (20 mL) was added MnO_2 (435 mg, 4.95 mmol), and the resulting mixture was refluxed for 12 hours. The mixture was filtered to remove excess MnO_2, and the filtrate was concentrated to give EXAMPLE 92 (138 mg, 100%) as a white solid. ESMS $(M+H)^+$ m/z: 419.

EXAMPLE 93

1-(4'-Methoxyphenyl)-5-N-(4'-(pyrrolidinocarbonyl)anilide)-1H-pyrazol-3-yl-carboxylic acid

[0222] 1-(4'-Methoxyphenyl)-5-N-(4'-(pyrrolidinocarbonyl)anilide)-1H-pyrazol-3-yl-carboxylic acid: To a solution of $AgNO_3$ (34 mg, 0.2 mmol) in H_2O (0.5 mL) was added NaOH (16 mg, 0.4 mmol), and a solution of 1-(4'-methoxyphenyl)-3-formaldehyde-1H-pyrazole-5-N-((4'-pyrrolidinocarbonyl)phenyl)carboxyamide (EXAMPLE 92, 42 mg, 0.1 mmol) in MeOH (0.5 mL) at 0°C. After being stirred at room temperature for 30 minutes, the mixture was carefully acidified with conc. HCl (35 mL) to pH-2, and concentrated to give a residue, which was purified by silica gel column chromatography with gradient solvents (CH_2Cl_2 to EtOAc) to give the title compound (25 mg, 58%). ESMS $(M+Na)^+$ m/z: 456.9.

EXAMPLE 94

1-(4'-Methoxyphenyl)-3-methylcarboxylate-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phenyl)carboxyamide

[0223] 1-(4'-Methoxyphenyl)-3-methylcarboxylate-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phenyl)carboxyamide: To a solution of 1-(4'-methoxyphenyl)-3-formaldehyde-1H-pyrazole-5-N-((4'-pyrrolidinocarbonyl)phenyl) carboxyamide (EXAMPLE 92, 42 mg, 0.1 mmol) in MeOH (1 mL) was added KCN (7.8 mg, 0.12 mmol), HOAc (7.2 mg, 0.12 mmol) and MnO_2 (120 mg, 0.83 mmol), and the resulting mixture was stirred at room temperature for 12 hours. The mixture was diluted with EtOAc (50 mL), washed with water (10 mLx3) and brine, and dried over $MgSO_4$. The solution was filtered, concentrated, and purified by silica gel column chromatography with EtOAc to give the title compound (38 mg, 85% yield). ESMS $(M+Na)^+$ m/z: 471.

EXAMPLE 95

1-(4'-Methoxyphenyl)-3-cyanomethyl-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phenyl)carboxyamide

[0224] 1-(4'-Methoxyphenyl)-3-cyanomethyl-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phenyl)carboxyamide: To a solution of 1-(4'-methoxyphenyl)-3-hydroxylmethyl-1H-pyrazole-5-N-((4'-pyrrolidinocarbonyl)phenyl)carboxyamide (120 mg, 0.29 mmol) in CH_2Cl_2 (15 mL) was added MsCl (48 mg, 0.43 mmol) and Et_3N (44 mg, 0.43 mmol). After being stirred at room temperature for 2 hours, the resulting mixture was concentrated. A solution of the residue in DMF (3 mL) was treated with NaCN (43 mg, 0.87 mmol) and stirred for 16 hours. To the reaction mixture was added EtOAc (50 mL) and water (5 mL), and the EtOAc layer was washed with brine (10 mLx5), dried over $MgSO_4$, concentrated, and purified on silica gel TLC plates eluted with EtOAc to give the title compound (57 mg, 46%). ESMS $(M+Na)^+$ m/z: 430.

EXAMPLE 96

2-(1'-(4"-Methoxyphenyl)-5'-(4"-pyrrolidinocarbonyl)anilide-1H-pyrazol-3'-yl)acetic acid

[0225] 2-(1'-(4"-Methoxyphenyl)-5'-(4"-Pyrrolidinocarbonyl)anilido-1H-pyrazol-3'-yl)acetic acid: To 1-(4'-methoxyphenyl)-3-cyanomethyl-1H-pyrazole-5-N-((4'-pyrrolidinocarbonyl)phenyl)carboxyamide (27 mg, 0.063 mmol) was added 6N HCl (1 mL), and the resulting mixture was stirred at 75 °C for 16 hours. The mixture was extracted with EtOAc and the organic layer was dried over $MgSO_4$, concentrated, and purified on silica gel TLC plates eluted with 20% MeOH in EtOAc to give the title compound (2 mg, 7%). MS(ES-) $(M-H)^+$ m/z: 447.

EXAMPLE 97

1-(4'-Methoxyphenyl)-3-bromomethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0226] 1-(4'-Methoxyphenyl)-3-hydroxylmethyl-1H-pyrazole-5-N-(2'-tert-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxyamide: To a solution of 4-(2'-tert-butylaminosulfonylphenyl)aniline (1.33 g, 4.3 mmol) in CH_2Cl_2 (40 mL) was added $AlMe_3$ (2M in hexane, 6.5 mmol) at 0 °C. After the mixture was stirred at room temperature for 30 minutes, a solution of 1-(4'-methoxyphenyl)-3-hydroxylmethyl-1H-pyrazole-5-ethylcarboxylate (1.09 g, 3.95 mmol) in CH_2Cl_2 (5 mL) was added, and the resulting mixture was refluxed for 6 hours and quenched with water (5 mL). The mixture was filtered through a pad of Celite, and the filtrate was washed with water and brine, and dried over $MgSO_4$. Filtration, concentration, and purification by silica gel column chromatography with gradient solvents (CH_2Cl_2 to EtOAc to 10% MeOH/EtOAc) gave the title compound (1.8 g, 85%). ESMS $(M+H)^+$ m/z: 535.

[0227] 1-(4'-Methoxyphenyl)-3-bromomethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide: To a solution of 1-(4'-methoxyphenyl)-3-hydroxylmethyl-1H-pyrazole-5-N-(2'-tert-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (880 mg, 2.49 mmol) in CH_2Cl_2 (100 mL) was added PBr_3 (675 mg, 2.49 mmol). The resulting mixture was stirred at room temperature for 2 hours and concentrated. The residue was treated with TFA (10 mL), refluxed for 2 hours, and then concentrated. The residue was dissolved in EtOAc (50 mL) and water (5 mL). The EtOAc layer was washed with brine (10 mL), dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography with gradient solvents (hexane to EtOAc) to give the title compound (800 mg, 90%). ESMS $(M+H)^+$ m/z: 541/543.

EXAMPLE 98

1-(4'-Methoxyphenyl)-3-aminomethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0228] 1-(4'-Methoxyphenyl)-3-aminomethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide: To a solution of 1-(4'-methoxyphenyl)-3-bromomethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (140 mg, 0.259 mmol) in a mixture solvents ($EtOH/CH_3CN/H_2O$ = 10:5:1, 20 mL) was added NaN_3 (50.5 mg, 0.776 mmol). After refluxing for 16 hours, the resulting solution was cooled to room temperature. A solution of $SnCl_2 \cdot 2H_2O$ (350 mg, 1.55 mmol) in MeOH (4 mL) was added to the above solution, and the resulting mixture was stirred at room temperature for 2 hours. The mixture was neutralized with 1N NaOH to pH 8-9, and extracted with EtOAc. The EtOAc layer was concentrated and purified on silica gel TLC plates eluted with 20% MeOH in CH_2Cl_2 to give the title compound (126 mg, ~100%). ESMS $(M+H)^+$ m/z: 478.1.

EXAMPLE 99

1-(4'-Methoxyphenyl)-3-(N-methylsulfonylamino)methyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide

[0229] 1-(4'-Methoxyphenyl)-3-(N-methylsulfonylamino)methyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide : To a solution of 1-(4'-methoxyphenyl)-3-aminomethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (15 mg, 0.031 mmol) in CH_2Cl_2 (1 mL) was added MsCl (3.6 mg, 0.035 mmol) and Et_3N (4.7 mg, 0.047 mmol). After stirring at room temperature for 2 hours, the resulting mixture was concentrated and purified on a silica gel TLC plate eluted with EtOAc-CH_2Cl_2 (1:1) to give the title compound (12 mg, 70%). HRMS $(M+H)^+$ calc. m/z: 556.1324, obs.: 556.1320.

EXAMPLE 100

1-(4'-Methoxyphenyl)-3-(imidazol-1-yl)methyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide

[0230] 1-(4'-Methoxyphenyl)-3-(imidazol-1-yl)methyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide: To a solution of 1-(4'-methoxyphenyl)-3-bromomethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (30 mg, 0.055 mmol) in CH_2Cl_2 (2 mL) was added imidazole (12 mg, 0.176 mg), and the resulting mixture was stirred at room temperature for 8 hours. The mixture was concentrated and purified on silica gel TLC plates eluted with CH_2Cl_2/EtOAc (1:3) to give the title compound. ESMS $(M+Na)^+$ m/z: 528.5.

EXAMPLE 101

1-(4'-Methoxyphenyl)-3-hydroxylmethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

AND EXAMPLE 102

1-(4'-Methoxyphenyl)-3-trifluoroacetylhydroxylmethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide

[0231] Preparation of a mixture of 1-(4'-methoxyphenyl)-3-hydroxylmethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide and 1-(4'-methoxyphenyl)-3-trifluoroacetylhydroxylmethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide: To 1-(4'-methoxyphenyl)-3-hydroxylmethyl-1H-pyrazole-5-N-(2'-tert-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (40 mg, 0.075 mmol) was added 25% TFA in CH_2CH_2 (6 mL), and the mixture was stirred at room temperature for 20 hours. The mixture was concentrated and purified by prep. HPLC to give EXAMPLE 101: 1-(4'-methoxyphenyl)-3-hydroxylmethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphenyl)carboxyamide (8 mg, 22%): ESMS $(M+H)^+$ m/z: 479; and EXAMPLE 102: 1-(4'-methoxyphenyl)-3-trifluoroacetylhydroxylmethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (18 mg, 42%): ESMS $(M+H)^+$ m/z: 575.

EXAMPLE 103

1-(4'-Methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-methylsulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0232] 1N-(4'-methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-5-methylpyrazole: To a solution of 2-bromo-5-methoxyphenyl methylcarboxylate (4.9 g, 20 mmol) in DMF (25 mL) was added 3-methyl-5-trifluoromethylimidazole (3.0 g, 20 mmol), CuBr (1 g, 7 mmol), and K_2CO_3 (2.76 g, 20 mmol). The mixture was stirred at 110 °C for 18 hours and diluted with EtOAc (150 mL). The mixture was filtered through a pad of Celite, and the filtrate was washed with water and brine (10 mLx5), and dried over $MgSO_4$. Filtration, concentration, and purification by silica gel column chromatography with hexane-CH_2Cl_2 (1:1) gave 1N-(4'-methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-5-methylpyrazole (3.17 g, 51%). ESMS $(M+H)^+$ m/z: 315.

[0233] 1N-(4'-methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-carboxylic acid: To a solution of 1N-(4'-methoxy-2-methoxycarbonylphenyl)-3-trifluoromethyl-5-methylpyrazole (2.54 g, 8.09 mmol) in CCl_4 (150 mL) was added NBS (2.88 g, 16.18 mmol), benzoyl peroxide (31 mg, 0.12 mmol), and AIBN (123 mg, 0.44 mmol), and the mixture was degassed and then filled with nitrogen. After refluxing under nitrogen for 24 hours, the mixture was cooled to 0 °C and filtered. The filtrate was concentrated to give a crude oil. To a solution of the crude oil in CH_3CN (50 mL) and water (20 mL) was added $KMnO_4$ (1.8 g, 11.4 mmol). The mixture was stirred at 95 °C for 1.5 hours and cooled to room temperature. A solution of Na_2SO_3 (5 g in 15 mL of water) and $NaHCO_3$ (5.5 g in 30 mL of water) was added, and the resulting mixture was filtered through a pad of Celite. The filtrate was extracted with ether, and the aqueous layer was carefully acidified with conc. HCl to pH 2 and extracted with EtOAc. The EtOAc layer was washed with brine (10 mL) and dried over $MgSO_4$. Filtration and concentration gave pure 1N-(4'-methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-carboxylic acid (1.2 g, 43.1%). ESMS $(M+H)^+$ m/z: 345.

[0234] 1-(4'-Methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-methylsulfonyl-[1,1']-biphen-4-yl)carboxyamide: To a solution of 1N-(4'-methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-carboxylic acid (344 mg, 1 mmol) in DMF (5 mL) was added PyBrop (559 mg, 1.2 mmol), and the mixture was stirred at room temperature for 30 minutes. After N,N-diisopropylethylamine (288 mg, 2.5 mmol) was added, the resulting mixture was stirred for 10 minutes, and then a solution of 4-(2'-methylsulfonylphenyl)aniline (265 mg, 1 mmol) was added. The resulting mixture was stirred at 90 °C for 16 hours, diluted with EtOAc (100 mL), washed with 1N HCl (20 mLx2), 10% $NaHCO_3$ (20 mLx2), water (10 mL), and brine (20 mLx4), dried over $MgSO_4$, and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL) and treated with DOWAX(1 g) for 30 minutes. The mixture was filtered and the filtrate was purified by silica gel column chromatography with gradient solvents (CH_2Cl_2 to EtOAc) to give the title compound (430 mg, 73%). ESMS $(M+H)^+$ m/z: 592.

EXAMPLE 104

1-(4'-Methoxy-2'-hydroxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-methylsulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0235] To a solution of 1-(4'-methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-methylsulfonyl-[1,1']-biphen-4-yl)carboxyamide (290 mg, 0.49 mmol) in MeOH (10 mL) was added aqueous NaOH (0.39 g in 5 mL of water), and the mixture was stirred at room temperature for 16 hours. After extracting with ether, the resulting aqueous solution was carefully acidified with conc. HCl to pH 2 and extracted with EtOAc. The EtOAc layer was dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography with EtOAc to give the title compound (110 mg, 50 %) as a white solid. ESMS $(M+H)^+$ m/z: 578.

EXAMPLE 105

1-(4'-Methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0236] To a solution of 1N-(4'-methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-carboxylic acid (344 mg, 1 mmol) in DMF (5 mL) was added PyBrop (559 mg, 1.2 mmol), and the mixture was stirred at room temperature for 30 minutes. N,N-diisopropylethylamine (288 mg, 2.5 mmol) was added and the resulting mixture was stirred for 10 minutes, and then a solution of 4-(2'-tert-butylaminosulfonylphenyl)aniline hydrochloride salt (358 mg, 1 mmol) was added. The resulting mixture was stirred at 90 °C for 16 hours and quenched with EtOAc (100 mL). The mixture was washed with 1N HCl (20 mLx2), 10% $NaHCO_3$ (20 mLx2), water (10 mL), and brine (20 mLx4), dried over $MgSO_4$, and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL) and treated with DOWEX (1 g) for 30 minutes, and

filtered. The filtrate was purified by silica gel column chromatography with gradient solvents (CH_2Cl_2 to EtOAc) to give 1-(4'-methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-tert-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (550 mg, 85%). ESMS $(M+H)^+$ m/z: 649.

[0237] To 1-(4'-methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-tert-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (200 mg) was added TFA (5 mL), and the resulting solution was refluxed for 2 hours. The mixture was concentrated and purified on silica gel TLC plates eluted with 10% EtOAc in CH_2Cl_2 to give the title compound (160 mg, 87%). ESMS $(M+H)^+$ m/z: 593.

EXAMPLE 106

1-(4'-Methoxy-2'-hydroxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-tert-butylaminosulfonyl-[1,1']-biphenyl)carboxyamide

[0238] To a solution of 1-(4'-methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-tert-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (350 mg, 0.54 mmol) in MeOH (5 mL) was added aqueous NaOH (90 mg in 5 mL of water), and the mixture was stirred at room temperature for 16 hours. After extracting with ether, the resulting aqueous solution was carefully acidified with conc. HCl to pH 2 and extracted with EtOAc. The EtOAc layer was dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography with EtOAc to give the title compound (210 mg, 61.3 %) as a white solid. ESMS $(M+H)^+$ m/z: 635.

EXAMPLE 107

1-(4'-Methoxy-2'-hydroxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0239] To 1-(4'-methoxy-2'-hydroxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-tert-butylaminosulfonyl-phenyl)-phenyl)carboxyamide (210 mg, 0.33 mmol) was added TFA (5 mL), and the resulting solution was refluxed for 1 hour. The mixture was concentrated and purified on silica gel TLC plates eluted with 10% MeOH in EtOAc to give the title compound (190 mg, 99%). ESMS $(M+H)^+$ m/z: 579.

EXAMPLE 108

1-(4'-Methoxy-2'-hydroxylmethylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0240] To a solution of 1-(4'-methoxy-2'-hydroxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-aminosulfonylphenyl)-phenyl)carboxyamide (210 mg, 0.36 mmol) in THF (5 mL) at 0 °C was added N,N-diisopropylethylamine (62 mg, 0.54 mmol) and isopropylchloroformate (freshly distilled, 46 mg, 0.38 mmol), and the resulting mixture was stirred at room temperature for 1.5 hours. $NaBH_4$ (30 mg, 0.79 mmol) was added and the mixture was stirred for 1 hour. The reaction was quenched with 1N HCl and stirred for 30 minutes. The mixture was diluted with EtOAc and the organic layer was washed with water and brine, dried over Na_2SO_4, and purified on silica gel TLC plates eluted with EtOAc to give the title compound (75 mg, 37%). ESMS $(M+Na)^+$ m/z: 586.9.

EXAMPLES 109 TO 115

[0241] **1N-(4'-Methoxyphenyl)-3-methylpyrazol-5-yl)ethylcarboxylate:** To a solution of 4-methoxyphenylhydrazine (8.65 g, 50 mmol) in HOAc (300 mL) at 80 °C was added oxime (ethyl 2-N-(methoxy)imino-4-oxopentanoate (see Example 1), 6 g, 32 mmol), and the mixture was refluxed for 18 hours and concentrated. The residue was dissolved in EtOAc (300 mL), washed with 10% NaOH (100 mL), water (100 mLx2), and brine (20 mLx2), dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography with CH_2Cl_2 to give partially purified product, which was recrystalized in hexane to give the title compound (10.5 g, 80%). ESMS $(M+H)^+$ m/z: 261.

[0242] **1N-(4'-Methoxyphenyl)-3-methylpyrazol-5-yl)carboxylic acid:** A solution of 1N-(4'-methoxyphenyl)-3-methylpyrazol-5-yl)ethylcarboxylate (5.9 g, 22.7 mmol) in THF (50 mL) was treated with 1N NaOH (50 mL) at room temperature for 24 hours. The aqueous layer of the mixture was carefully acidified with conc. HCl to pH 2 and extracted with EtOAc. The EtOAc layer was dried, concentrated, and purified by silica gel column chromatography with gradient solvents (CH_2Cl_2 to EtOAc) to give the title compound (3.7 g, 66.3%). ESMS $(M-H)^+$ m/z: 245.

[0243] **Preparation of a Examples 109-115 via a library:** To a solution of 1N-(4'-methoxyphenyl)-3-methylpyrazol-5-yl)carboxylic acid (450 mg, 1.94 mmol) in CH_3CN (30 mL) was added $SOCl_2$ (1.4 g, 11.6 mmol). The resulting mixture

was refluxed for 1.5 hours and then concentrated. A solution of the residue in THF (38 mL) was divided into portions and added to solutions of anilines or amines (0.1 mmol/sample/well) and DMAP (12.4 mg/well) in THF (1 mL/well) in a 96 well polyfiltronics filter plate. The 96 well polyfiltronics filter plate containing the reaction mixtures was shaken at room temperature for 2 days. To each solution/well was added a suspension of DOWEX (0.2 g) in CH_2Cl_2 (0.4 mL) and the resulting mixtures were shaken for one hour. The mixtures were filtered and the filtrates were carefully collected and dried under vacuum to give the library.

EXAMPLE 109

[0244] 1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-sec-butyl)phenyl)carboxyamide: ESMS $(M+H)^+$ m/z: 404.

EXAMPLE 110

[0245] 1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-(3"-methyl-3"-pyrazolin-5"-one-2"-yl)phenyl)carboxyamide: ESMS $(M+H)^+$ m/z: 364.

EXAMPLE 111

[0246] 1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-(6"-methylbenzothiazol-2"-yl)phenyl)carboxyamide: ESMS $(M+H)^+$ m/z: 455.

EXAMPLE 112

[0247] 1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(3', 4'-dibromophenyl)carboxyamide: ESMS $(M+H)^+$ m/z: 364.

EXAMPLE 113

[0248] 1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-n-butyl)phenyl)carboxyamide: ESMS $(M+H)^+$ m/z: 464.

EXAMPLE 114

[0249] 1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-(4"-methylpiperidino)phenyl)carboxyamide: ESMS $(M+H)^+$ m/z: 405.

EXAMPLE 115

[0250] 1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-(2"-methylimidazol-1"-yl)phenyl)carboxyamide: ESMS $(M+H)^+$ m/z: 388.

EXAMPLE 116

[0251] 3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-carboxy(N-methylimidazo-2-yl)phenyl) carboxyamide

[0252] Part A. To 4-nitro-1-(2'-N-methylimidazoyl)benzene (0.58 g, 2.51 mmol), prepared from 4-nitrobenzoyl chloride and 1-methylimidazole by the method of Regel, E. et al., Liebigs Ann. Chem. (1977) 145, was added ethanol (50 mL), trifluoroacetic acid (1 mL) and 10% palladium on carbon (60 mg). The mixture was hydrogenated on the Parr at 40 psi for 0.5h. The reaction mixture was filtered and concentrated. The recovered aniline salt was dissolved in water and extracted with ether. The aqueous layer was made basic with 1N NaOH, extracted with ethyl acetate and dried ($MgSO_4$) and evaporated to give 0.35 g (70%) of the aniline. MS (AP+) 202.1 $(M+H)^+$.

[0253] Part B. To 1-(4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-carboxylic acid (0.25 g, 0.87 mmol) in CH_2Cl_2 (15 mL) was added oxalyl chloride (0.1 mL, 1.14 mmol) and several drops of DMF. The reaction was stirred for 24h, then concentrated. The aniline from Part A (0.175 g, 0.87 mmol), DMAP (0.27 g, 2.2 mmol), and fresh CH_2Cl_2 (20 mL) were added to the acid chloride and the reaction was stirred for 24h. The mixture was concentrated and the residue was dissolved in EtOAc (10 mL) and TFA (0.1 mL), concentrated and purified by reverse phase HPLC and lyophilized to afford the title compound 60 mg (11%); ^1H NMR (DMSO-d6) δ 10.97 (s, 1H), 8.30 (d,j=8.80 Hz, 2H) , 7.80 (d,j=8.80

Hz, 2H), 7.63 (d,j=10.2 Hz, 2H), 7.48 (d,j=9.20 Hz, 2H), 7.22 (s, 1H), 7.07 (d,j=8.80 Hz, 2H), 3.98 (s, 3H), 3.82 (s, 3H) ppm; HRMS $(M+H)^+$ $C_{23}H_{19}F_3N_5O_3$ 470.1443.

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-hydroxymethyl(2-(imidazol-2-yl)phenyl))) carboxyamide

AND EXAMPLE 118

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-hydroxymethyl(2-(1-benzyl-imidazol-2-yl) phenyl)))carboxyamide

AND EXAMPLE 119

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-(N-(4-(2-carboxy(imidazol-2-yl)phenyl)))carboxyamide

[0254] Part A: To 4-nitro-1-(2'-N-benzylimidazoyl)benzene (0.47 g, 1.53 mmol), prepared from 4-nitrobenzoyl chloride and 1-benzylimidazole by the method of Regel,E. et al., Liebigs Ann: Chem. (1977) 145, was added EtOAc (15 mL) and stannous chloride (0.86 g, 3.80 mmol). The reaction was heated to reflux for 2h then stirred at rt for 18h. An additional 0.3 g of stannous chloride was added and the reaction stirred 3h. The reaction was cooled to 0°C, quenched with 6M NaOH, and extracted with EtOAc and dried (Na_2SO_4) to afford 0.4 g (95%) orange solid. MS $(M+H)^+$ 278.2 (AP+).

[0255] Part B: The benzyl compound from part A (0.229 g, 0.4 mmol) was hydrogenated on the Parr in EtOH (30 mL) and TFA (0.5 mL) with 30 mg 10% Pd/C at 40psi for 0.5h. The reaction was filtered, concentrated and purified via reverse phase HPLC to afford the above mentioned titled compounds, respectively.

[0256] EXAMPLE 117: 5.3 mg (2.2%) ^1H NMR(DMSO-d6)δ: 10.75 (s, 1H), 7.66 (d,j=8.40 Hz, 2H), 7.55 (m+d,j=6.60 Hz, 3H), 7.45 (d,j=9.10 Hz, 2H), 7.40 (d,j=8.40 Hz, 2H), 7.05 (d,j=8.80 Hz, 2H), 6.55 (brd s, 2H), 6.00 (d,j=4.0 Hz, 1H), 3.81 (3H,s) ppm. HRMS for $(M+H)^+$ $C_{22}H_{19}F_3N_5O_3$ 458.1437,

[0257] EXAMPLE 118: 73 mg (25%) ^1H NMR (DMSO-d6)δ: 10.76 (s, 1H), 7.69 (s, 1H), 7.64 (d,j=1.90 Hz, 1H), 7.63 (d,j=8.80 Hz, 2H), 7.55 (s, 1H), 7.34 (d,j=5.80 Hz, 2H), 7.32 m, 5H), 7.19 (brd, 1H), 7.10 (dd,j=2.20, 5.80 Hz, 2H), 7.06 (d,j=9.20 Hz, 2H), 6.24 (s, 1H), 5.38 (d,j=3.70 Hz, 2H), 3.81 (s, 3H) ppm; HRMS $(M+H)^+$ for $C_{29}H_{25}F_3N_5O_3$ 548.1923,

[0258] **EXAMPLE 119**: 15 mg (6.2%) ^1H NMR (DMSO-d6)δ: 10.99 (s, 1H), 8.56 (d,j=8.50 Hz, 2H), 7.84 (d,j=8.80 Hz, 2H), 7.64 (s, 1H), 7.48 (d,j=8.80 Hz, 2H), 7.41 (s, 2H), 7.31 (m, 1H), 7.07 (m+d,j=8.80 Hz, 3H), 3.82 (s, 3H) ppm; HRMS (M+H)+ for C22H17F3N5O3 456.1271.

EXAMPLE 120

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-(4-methoxyphenyl)amino-(2-thiazolyl)methyl) phenyl)))carboxyamide

AND EXAMPLE 121

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-(N-(4-(2-carboxy-(4,5-dihyrothiazol-2-yl)phenyl))) carboxyamide

[0259] Part A: p-Aminobenzaldehyde (135 mg, 1.11 mmol), and TEA (0.155 mL, 1.11 mmol) were added to 3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid chloride (0.34 g, 1.11 mmol) in CH_2Cl_2 (10 mL). The reaction was stirred for 18h, then concentrated. Purification by chromatography on silica gel using 2:1 hexanes/EtOAc as eluent to give 0.16 g (37%) pale yellow solid. MS (ESI) $(M-H)^+$ 388.1.

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-(4-methoxyphenyl)amino-(2-thiazolyl)methyl)-phenyl)))carboxyamide:

[0260] Part B: To thiazole (0.1 mL, 1.43 mmol) in THF(6 mL) cooled to-40°C was added n-BuLi (0.6 mL, 1.43 mmol) and stirred for 1.5h. To the aldehyde from part A (0.14 g, 0.36 mmol) in benzene (10 mL) and MeOH (5 mL) was added 4A molecular sieves and p-anisidine (44 mg, 0.36 mmol) and the mixture was heated to reflux for 15 minutes. The mixture was filtered and concentrated to give the imine. To the imine in THF (5 mL) at-78°C was added the thiazole anion by cannula. The reaction was stirred at 0°C for 0.5h then quenched with 1M $KHSO_4$ (0.4 mL). The product was extracted with EtOAc and dried ($MgSO_4$). Purification by chromatography on silica gel using 1:2 Hexanes/EtOAc af-

forded 0.113 g (54%) of the title compound; MS $(M-H)^+$ 578.1; ^1H NMR ($CDCl_3$) δ: 7.74 (d,j=3.30 Hz, 1H), 7.50 (d, j=15.4 Hz, 2H), 7.41 (brd s, 5H), 7.27 (d,j=3.30 Hz, 1H), 7.12 (s, 1H), 7.01 (d,j=9.20 Hz, 2H), 6.74 (d,j=8.80 Hz, 2H), 6.59 (d,j=8.80 Hz, 2H), 5.71 (d,j=3.60 Hz, 1H), 4.56 (d,j=3.60 Hz, 1H), 3.85 (s, 3H), 3.71 (s, 3H) ppm.

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-(N-(4-(2-carboxy-(4,5-dihyrothiazol-2-yl)phenyl))) carboxyamide:

[0261] Part C: To the product from part B (98 mg, 0.17 mmol) in acetonitrile (10 mL)at 0°C was added cerric ammonium nitrate (0.185 g, 0.34 mmol) in water (10 mL). The reaction was stirred for 10 minutes, then concentrated. The residue was dissolved in EtOAc and washed with aqueous sodium bisulfite and dried ($MgSO_4$). The product was purified by silica gel chromatography, reverse phase HPLC and lyophilized to afford the title compound (10 mg, 12%). ^1H NMR ($CDCl_3$)δ: 8.54 (d,j=8.80 Hz, 2H), 8.09 (d,j=2.90 Hz, 1H), 7.73 (d,j=3.30 Hz, 1H), 7.66 (s, 1H), 7.59 (d,j=8.80 Hz, 2H), 7.48 (d,j=8.80 Hz, 2H), 7.19 (s, 1H), 7.05 (d,j=9.20 Hz, 2H), 3.88 (s, 3H) ppm; MS $(M+H)^+$ 473.2 (AP+).

EXAMPLE 122

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-4-(2-(4', 5'-dihydro-1'H-imidazol-2'yl)phenyl) carboxyamide

AND EXAMPLE 123

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(4-(N-2'-aminoethylenecarboxyamide)phenyl) carboxyamide

[0262] To trimethylaluminum (1.2 mL, 2M in heptane), cooled to 0°C was added ethylenediamine (57 mg, 0.95 mmol) and the mixture was stirred for 15 minutes. A suspension of ethyl-3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-carboxyphenyl)carboxyamide previously prepared (0.2 g, 0.47 mmol) in toluene (10 mL) was added. The reaction was heated to 50°C for a total of 9h and room temperature for 18h. The reaction was quenched with ice water, filtered and concentrated. The aqueous layer was extracted with CH_2Cl_2 which was then extracted with 1N HCl. The acid layer was basified and extracted with EtOAc and dried ($MgSO_4$). Purification by reverse phase HPLC and freeze drying afforded 56 mg (22%)of the imidazoline (EXAMPLE 122) and 7 mg (3%) of the ring open amide (EXAMPLE 123).
[0263] EXAMPLE 122: For the imidazoline: ^1H NMR (DMSO-d6) δ: 11.10 (s, 1H), 10.40 (s, 1H), 7.91 (d,j=3.60 Hz, 4H), 7.64 (s, 1H), 7.48 (d,j=8.80 Hz, 2H), 7.07 (d,j=9.20 Hz, 2H), 3.99 (s, 4H), 3.82 (s, 3H) ppm; MS (ESI) 430.2 $(M+H)^+$.
[0264] EXAMPLE 123: For the amide: ^1H NMR (DMSO-d6) δ:10.88 (s, 1H), 8.59 (t,j=5.50 Hz, 1H), 7.87 (d,j=8.80 Hz, 2H), 7.79 (m, 2H), 7.75 (d,j=8.80 Hz, 2H), 7.61 (s, 1H), 7.47 (d,j=9.2 Hz, 2H), 7.06 (d,j=8.80 Hz, 2H), 3.82 (s, 3H), 3.51 (q,j=5.50 Hz, 2H), 2.98 (q,j=5.90 Hz, 2H) ppm; MS (ESI) 448.2 $(M+H)^+$.

EXAMPLE 124

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-[4-(1,4,5,6-tetrahydro-pyrimid-2-yl)-phenyl] carboxyamide

[0265] Ethyl-3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-carboxyphenyl)carboxyamide (0.2 g, 0.48 mmol) and 1,3-diaminopropane (70 mg, 0.95 mmol) were coupled as described above. Purification by reverse phase HPLC and freeze drying afforded 20 mg (7.5%). ^1H NMR (DMSO-d6) δ: 11.0 (s, 1H), 10.3 (s, 1H), 7.86 (d,j=8.80 Hz, 2H), 7.72 (d,j=8.80 Hz, 2H), 7.63 (s, 1H), 7.48 (d,j=9.20 Hz, 2H), 7.06 (d,j=9.20 Hz, 2H), 3.82 (s, 3H), 3.40 (m, 4H), 1.96 (t, 2H); HRMS for $C_{22}H_{21}F_3N_5O_2$ fnd 444.1646.

EXAMPLE 125

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-[4-(N-methyl-4,5,6-trihydro-pyrimid-2-yl)-phenyl] carboxyamide

[0266] Ethyl-3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-carboxyphenyl)carboxyamide (0.2 g, 0.48 mmol) and N-methyl-1, 3-propanediamine (0.1 mL, 0.95 mmol) were coupled as described above. Purification by reverse phase HPLC and freeze drying afforded 58 mg (21%). ^1H NMR (DMSO-d6) δ:9./0 (s, 1H), 7.85 (d,j=8.80 Hz, 2H), 7.62 (d,j=9.20 Hz, 2H), 7.55 (s, 1H), 7.47 (d,j=9.20 Hz, 2H), 7.07 (d,j=9.20 Hz, 2H), 3.82 (s, 3H), 3.57 (t,j=5.50 Hz, 2H), 3.39 (m, 2H), 2.97 (s, 3H), 2.05 (t,j=5.50 Hz, 2H) ppm.

EXAMPLE 126

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-1-(2-fluoro-4-imadazolinephenyl)carboxyamide

[0267] Part A: To 3-fluoro-4-nitrobenzoic acid (2.81 g, 15 mmol) in CH_2Cl_2 (75 mL) was was added oxalyl chloride (1.72 mL, 19.7 mmol) and several drops of DMF. The reaction was stirred 6h, stripped and ethanol (20 mL) was added. After 18h the ethanol was removed and EtOAc (30 mL) and stannous chloride (13.7 g, 61 mmol) were added. The reaction was heated to reflux for 2h, cooled and quenched with sat'd $NaHCO_3$. Extraction with EtOAc and drying ($MgSO_4$) afforded 2.7 g (97%) of the aniline.

[0268] Part B: To 1-(4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-carboxylic acid (0.21 g, 0.73 mmol) in CH_2Cl_2 (15 mL) was added oxalyl chloride (0.08 mL, 0.95 mmol) and several drops of DMF. The reaction was stirred for 24h, then concentrated. The acid choride, DMAP (0.27 g, 2.20 mmol), and the aniline from Part A (134 mg, 0.73 mmol) were combined in fresh CH_2Cl_2 and stirred 18h. The reaction mixture was washed with 1N HCl, sat'd $NaHCO_3$, brine and dried ($MgSO_4$). Purification by chromatography on silica gel using 1:1 hexanes/EtOAc as eluent afforded 254 mg (79.6%). ^1H NMR ($CDCl_3$) δ: 8.44 (t,j=8.10 Hz, 1H), 7.89 (d,j=3.30 Hz, 1H), 7.84 (d,j=9.60 Hz, 1H), 7.77 (dd,j=11.40, 1.50 Hz, 1H), 7.46 (d,j=9.10 Hz, 2H), 7.20 (s, 1H), 7.04 (d,j=8.80 Hz, 2H), 4.39 (q,j=7.0 Hz, 2H), 3.88 (s, 3H), 1.41 (t, j=6.90 Hz, 3H) ppm.

[0269] Part C: To trimethylaluminum (0.57 mL, 2M in heptane), cooled to 0°C was added ethylenediamine (27.6 mg, 0.46 mmol) and the mixture was stirred for 15 min. A suspension of ethyl-3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-carboxy-2-fluorophenyl)carboxyamide (0.1 g, 0.23 mmol) in toluene (10 mL) was added. The reaction was heated to 50°C for 18h and then, was quenched with ice water, filtered and concentrated. The aqueous layer was extracted with CH_2Cl_2 which was then extracted with 1N HCl. The acid layer was basified and extracted with EtOAc and dried ($MgSO_4$). Purification by reverse phase HPLC and lyophilization afforded 26 mg (20%). ^1H NMR (DMSO-d6) δ 10.90 (s, 1H), 10.55 (s, 1H), 8.10 (t,j=8.06 Hz, 1H), 7.93 (dd,j=11.0, 1.5 Hz, 1H), 7.80 (d,j=8.79 Hz, 1H), 7.64 (s, 1H), 7.47 (d,j=9.15 Hz, 2H), 7.06 (d,j=8.80 Hz, 2H), 4.01 (s, 4H), 3.81 (s, 3H) ppm; HRMS for $C_{21}H_{18}F_4O_2N_5$ found 488.1393.

EXAMPLE 127

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-1-(2-fluoro-4-N-methylimadazolinephenyl) carboxyamide

[0270] N-Methylethylenediamine (52 mg, 0.71 mmol) and ethyl-3-trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-carboxy-2-fluorophenyl)carboxyamide (150 mg, 0.35 mmol) were coupled by the same procedure as the previous example. Purification by reverse phase HPLC and lyophilization afforded 54 mg (27%). ^1H NMR (DMSO-d6) δ: 10.90 (s, 1H), 8.03 (t,j=8.10 Hz, 1H), 7.74 (dd,j=11.0, 1.5 Hz, 1H), 7.63 (s, 1H), 7.56 (d,j=9.90 Hz, 1H), 7.47 (d,j=8.80 Hz, 2H), 7.05 (d,j=8.80 Hz, 2H), 4.06 (m, 2H), 3.95 (m, 2H), 3.80 (s, 3H), 3.08 (s, 3H) ppm; MS (ESI) 462.3 $(M+H)^+$; Analysis calc'd for $C_{22}H_{19}F_4N_5O_2$ (TFA)1.4 (H20)C:46.61 H:3.53 N:10.96, found C:46.68 H:3.29 N:10.91.

EXAMPLE 128

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-[4-(4, 5-dihydro-1-N-methyl-imidazo-2-yl)phenyl] carboxyamide

AND EXAMPLE 129

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-[4-carbonylquanidine)phenyl]carboxyamide

[0271] Part A: To a dichloromethane solution (50 mL) of N-4'-methoxyphenyl-3-trifluromethyl-pyrazole-5-carboxylic acid (2 g, 6.99 mmol) was added oxalyl chloride (1.36 g, 10.48 mmol) and a few drops of DMF. The reaction mixture was stirred at room temperature for 3h then evaporated to a pale yellow solid and redissolved in dichloromethane (50 mL). To this solution was then added methyl-4-amino-benzoate (1 g, 6.99 mmol) and DMAP (2.1 g, 17.47 mmol). The reaction mixture was stirred at room temperature overnight, quenched with dil HCl (50 mL) and extracted organics with ethylacetate (2x100 mL), dried ($MgSO_4$) and evaporated to a yellow solid. Purification of the crude coupled product via flash silica gel chromatography (hexane:ethylacetate 7:3) afforded desired coupled precursor as colorless crystals (1.9 g). LRMS (ESI) m/z 420.0 (100). ^{1}HNMR($CDCl_3$): δ 8.019 (d, J=8.8, 2H); 7.617 (s, 1H); 7.480 (m, 4H); 7.158 (s, 1H); 7.03 (d, J=8.8, 2H); 3.90 (s, 3H); 3.87 (s, 3H) ppm.

[0272] **1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-[4-(4, 5-dihydro-1-N-methyl-imidazo-2-yl)phe-**

nyl]carboxyamide: Part B: The product from part A (0.2 g, 0.048 mmol) in dichloromethane (50 mL) was subjected to treatment with N1-methylethylenediamine (0.071 g, 0.099 mmol) followed by trimethylaluminum (1.23 mL, 2.45 mmol). The reaction mixture was stirred at room temperature overnight then quenched with dil HCl (5 mL). The product was concentrated *in vacuo* and purified via preparation HPLC (acetonitrile/water, 2%TFA). Lyophilization afforded colorless crystals (0.167 g) of the desired product. LRMS (ESI) m/z 444.2 (100). HRMS: $(M+H)^+$ calc. 444.1647, found 444.1644. ^{1}HNMR(DMSO-d_6): δ 11.07 (s, 1H); 10.12 (s, 1H); 7.88 (d, J=8.8, 2H); 7.71 (d, J=8.8, 2H); 7.63 (s, 1H); 7.47 (m, 2H): 7.06 (m, 2H): 4.05 (m, 2H): 3.89 (m, 2H); 3.82 (s, 3H): 3.09 (s, 3H) ppm. **1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-[4-carbonylguanidine)phenyl]carboxyamide:** Part C: The product from part A (150 mg, 0.358 mmol) was subjected to the standard Weinreb methodology described above with guanidine hydrochloride (103 mg, 1.074 mmol) and trimethylaluminum (103 mg, 1.432 mmol) in dichloromethane (10 mL). The mixture was stirred at ambient temperature for 18h and quenched with 1N hydrochloric acid (5 mL). The slurry was then basified (pH 9, sat. sodium bicarbonate). The organics were extracted with dichloromethane (3x100 mL) and dried (Na_2SO_4). Evaporation of the solvent followed by purification via reverse phase Prep HPLC and lyophilization then afforded the desired acylguanidyl compound as colorless crystals. LRMS(ESI) m/z 447.2 (100); HRMS $(M+H)^+$ 447.1392 (calc.), 447.1391 (obs); ^{1}HNMR(DMSO) δ: 11.20 (s, 1H); 11.00 (s, 1H); 8.33 (brd, 4H); 7.98 (d, J=8.79, 2H); 7.88 (d, J=8.79, 2H); 7.64 (s, 1H): 7.48 (d, J=8.79, 2H); 7.07 (d, J=9.16, 2H); 3.82 (s, 3H) ppm.

EXAMPLE 130

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-[4-(pyrimidin-2-yl)phenyl]carboxyamide

[0273] Part A: Standard Suzuki coupling of the 4-trifluoromethylphenylboronic acid (0.88 g, 3.77 mmol) and 2-bromopyrimidine (0.5 g, 3.144 mmol) afforded the coupled product (0.47 g). LRMS(ESI) m/z 268.1 (100); ^{1}HNMR ($CDCl_3$) δ: 8.82 (d, J=5.1, 2H): 8.52 (d, J=8.8, 2H): 7.96 (brd, 1H): 7.73 (d, J=8.8, 2H); 7.23 (t, J=4.8, 1H) ppm; Hydrolysis of this compound with 1N NaOH/EtOH (1:1, 10 mL for 18 h, followed by purification using flash chromatograghy (4:1/Hexanes:Ethyl acetate) afforded the desired anilinopyrimidyl precursor (0.24 g). LRMS(NH_3-Cl) m/z 172.2 (100); ^{1}HNMR($CDCl_3$) δ: 8.73 (d, J=5.1, 2H); 8.28 (m, 2H); 7.06 (t, J=5.1, 1H); 6.76 (m, 2H); 3.94 (brd, 2H) ppm.

[0274] 1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-[4-(pyrimidin-2-yl)phenyl]carboxyamide: Part B: Standard DMAP (0.23 g, 1.92 mmol) coupling of the compound obtained in part A (0.13 g, 0.77 mmol) with trifluoromethylpyrazole acid chloride (0.22 g, 0.77 mmol of carboxylic acid) obtained previously afforded the desired coupled product which was purified via silica gel flash chromatography (hexane/ethyl acetate, 1:1) to afford the titled compound as colorless crystals (0.14 g).LRMS(ESI) m/z 440.1 (100); HUMS $(M+H)^+$ 440.1334 (calc.) 440.1333 (obs); ^{1}HNMR (DMSO-D6) δ: 10.89 (s, 1H): 8.88 (d, J=4.8, 2H): 8.39 (d, J=8.8, 2H): 7.82 (d, J=8.4, 2H): 7.61 (s, 1H): 7.48 (d, J=8.8, 2H): 7.43 (t, J=4.7, 1H): 7.07 (d, J=9.2, 2H): 3.82 (s, 3H) ppm.

EXAMPLE 141

1-[(4-Methoxy)phenyl]-3-(ethoxycarbonyl)-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide

[0275] 1-[(4-methoxy)phenyl]-3,5-dimethylpyrazole. To a solution of 4-methoxyphenylhydrazine hydrochloride (118.7 g, 0.68 mol) in 300 mL of glacial acetic acid was added 2, 4-pentanedione (68.0 g, 0.68 mol). The resulting solution was stirred at 100°C for 18 h and then was cooled and concentrated *in vacuo*. The residue was dissolved in ethyl acetate, filtered through a pad of silica gel and concentrated to afford 131 g (95%) of the title compound, which was used without purification. LRMS (NH_4-Cl): 203.3 $(M+H)^+$.

[0276] 1-[(4-methoxy)phenyl]pyrazole-3,5-dicarboxylic acid. To a suspension of 1-[(4-methoxy)phenyl]-3, 5-dimethylpyrazole (131 g, 0.65 mol) in 400 mL of water was added potassium permanganate (410 g, 2.6 mol). This mixture was heated to 70°C and was stirred for 1 h. The reaction was filtered and the filter cake was washed with hot water. The filtrate was acidified with HCl and then was extracted twice with ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$) and concentrated. The residue was triturated with chloroform and filtered to afford 39.7 g (23%) of the title compound. LRMS (ES-): 260.9 $(M-H)^-$.

[0277] Dimethyl 1-[(4-methoxy)phenyl]pyrazole-3,5-dicarboxylate. A solution of 1-[(4-methoxy)phenyl]pyrazole-3, 5-dicarboxylic acid (39.7 g, 0.15 mol) in 300 mL of anhydrous methanol was cooled to 0°C and then anhydrous HCl was bubbled through the solution for 15 minutes through a gas dispersion tube. The flask was tightly stoppered and the reaction was allowed to stir at ambient temperature for 24 h. The volatiles were removed *in vacuo*. The residue was dissolved in ethyl acetate, filtered through a pad of silica gel and concentrated *in vacuo* to afford 32.8 g (74%) of the title compound which was used without purification. LRMS (NH_4-Cl): 291.2 $(M+H)^+$.

[0278] 1-[(4-methoxy)phenyl]-5-(methoxycarbonyl)pyrazole-3-carboxylic acid. To a solution of dimethyl 1-[(4-methoxy)phenyl]pyrazole-3, 5-dicarboxylate (32.7 g, 110 mmol) in 50 mL of dioxane and 100 mL of water was

added concentrated sulfuric acid (1.50 mL, 28.2 mmol). The resulting solution was stirred at 100°C for 18 h and then cooled to room temperature. The reaction was made basic with potassium carbonate and then extracted with ether to remove unreacted diester. The aqueous layer was acidified with HCl and was extracted twice with ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$) and concentrated to afford 19.2 g (63%) of the title compound along with 5.0 g (15%) of unreacted starting material. The title compound was used without further purification. LRMS (ES-): 274.9 $(M-H)^-$.

[0279] 1-[(4-methoxy)phenyl]-3-(ethoxycarbonyl)-5-(methoxycarbonyl)pyrazole. A solution of 1-[(4-methoxy)phenyl]-5-(methoxycarbonyl)pyrazole-3-carboxylic acid (7.50 g, 27.1 mmol) in 50 mL of thionyl chloride was stirred at 80°C for 1 h. The volatiles were then removed and the residue was azeotroped with 20 mL of toluene and dried *in vacuo*. The residue was dissolved in 100 mL of tetrahydrofuran and then there was added diisopropylethylamine (11.8 mL, 67.9 mmol) and absolute ethanol (3.2 mL, 54.3 mmol). The reaction mixture was allowed to stir at ambient temperature for 24 h. The volatiles were removed and the residue was dissolved in ethyl acetate. This solution was filtered through a pad of silica gel and was concentrated *in vacuo* to afford 3.7 g (45%) of the title compound which was used without purification. LRMS (DCI): 305.1 $(M+H)^+$.

[0280] 1-[(4-methoxy)phenyl]-3-(ethoxycarbonyl)pyrazole-5-carboxylic acid. To a solution 1-[(4-methoxy)phenyl]-3-(ethoxycarbonyl)-5-(methoxycarbonyl)pyrazole (4.0 g, 13.2 mmol) in 40 mL of tetrahydrofuran and 20 mL of water was added an aqueous solution of lithium hydroxide monohydrate (0.55 g, 13.2 mmol). The reaction was allowed to stir at ambient temperature for 1 h. The tetrahydrofuran was removed *in vacuo* and the aqueous was extracted with ether to remove unreacted diester. The aqueous layer was acidified with HCl and extracted with ethyl acetate. The organics were washed with brine, dried ($MgSO_4$) and concentrated to afford 3.2 g (84%) of the title compound, which was used without further purification. LRMS (ES-): 289.0 $(M-H)^-$.

[0281] 1-[(4-methoxy)phenyl]-3-(ethoxycarbonyl)-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide. A solution of 1-[(4-methoxy)phenyl]-3-(ethoxycarbonyl)pyrazole-5-carboxylic acid (3.2 g, 11.1 mmol) in 20 mL of thionyl chloride was stirred at 80°C for 1 h. The volatiles were then removed and the residue was azeotroped with 20 mL of toluene and dried *in vacuo*. The residue was dissolved in 50 mL of methylene chloride and then there was added triethylamine (4.6 mL, 33.3 mmol) and 4-(*N*-pyrrolidinocarbonyl)aniline (3.2 mL, 54.3 mmol). The reaction mixture was allowed to stir at ambient temperature for 4 h. The volatiles were removed and the residue was dissolved in ethyl acetate, washed sequentially with 10% aq HCl and brine, dried ($MgSO_4$), filtered through a short pad of silica gel and concentrated to afford 2.5 g (50%) of the title compound. A small portion was further purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford the title compound as a white powder. LRMS (ES+): 463.1 $(M+H)^+$.

EXAMPLE 142

1-[(4-Methoxy)phenyl]-3-(carboxyamide)-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide

[0282] 1- [(4-methoxy)phenyl]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide-3-carboxylic acid. To a solution 1-[(4-methoxy)phenyl]-3-(ethoxycarbonyl)-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide (2.05 g, 4.43 mmol) in 10 mL of THF and 10 mL of water was added potassium hydroxide (0.32 g, 5.76 mmol). The resulting solution was stirred at ambient temperature for 18. The THF was removed *in vacuo* and the aqueous was extracted with ether to remove unreacted ester. The aqueous layer was acidified with HCl and extracted with ethyl acetate. The organics were washed with brine, dried ($MgSO_4$) and concentrated to afford 1.1 g (57%) of the title compound, which was used without further purification. LRMS (ES-): 433.0 $(M-H)^-$.

[0283] 1-[(4-methoxy)phenyl]-3-(carboxyamide)-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide. To a solution of 1-[(4-methoxy)phenyl]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide-3-carboxylic acid (117 mg, 0.27 mmol) in 10 mL of 1:1 THF/CH_3CN was added triethylamine (0.056 mL, 0.40 mmol) and *iso*-butyl chloroformate (0.038 mL, 0.30 mmol). After stirring at ambient temperature for 30 min, there was added methanolic ammonia solution (1.34 mL of a 2.0 M solution of ammonia in methanol, 2.7 mmol). The reaction was stirred for 1 h and then the volatiles were removed. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 50 mg (43%) of the title compound as a white powder. LRMS (ES+): 434.1 $(M+H)^+$.

EXAMPLE 143

1-[(4-Methoxy)phenyl]-3-[(2-hydroxyethyl)carboxyamide]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl) carboxyamide

[0284] To a solution of 1-[(4-methoxy)phenyl]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide-3-car-

boxylic acid (110 mg, 0.25 mmol) in 5 mL of acetonitrile was added triethylamine (0.053 mL, 0.38 mmol) and *iso*-butyl chloroformate (0.036 mL, 0.28 mmol). After stirring at ambient temperature for 30 min, there was added ethanolamine (0.06 mL, 1.01 mmol). The reaction was stirred for 1 h and then the volatiles were removed. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 80 mg (67%) of the title compound as a white powder. LRMS (ES+): 478.0 $(M+H)^+$.

EXAMPLE 144

1-[(4-Methoxy)phenyl)-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide-3-hydroxamic acid

[0285] To a solution of 1-[(4-methoxy)phenyl]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide-3-carboxylic acid (100 mg, 0.23 mmol) in 5 mL of acetonitrile was added triethylamine (0.064 mL, 0.46 mmol) and *iso*-butyl chloroformate (0.030 mL, 0.23 mmol). After stirring at ambient temperature for 30 min, there was added hydroxylamine hydrochloride (16 mg, 0.23 mmol). The reaction was stirred for 1 h and then the volatiles were removed. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 28 mg (27%) of the title compound as a white powder. LRMS (ES-): 562.1 $(M-H+TFA)^-$.

EXAMPLE 145

1-[(4-Methoxy)phenyl]-3-[phenylcarboxyamide]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl) carboxyamide

[0286] To a solution of 1-[(4-methoxy)phenyl]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide-3-carboxylic acid (100 mg, 0.23 mmol) in 5 mL of acetonitrile was added triethylamine (0.064 mL, 0.46 mmol) and *iso*-butyl chloroformate (0.030 mL, 0.23 mmol). After stirring at ambient temperature for 30 min, there was added aniline (0.02 mL, 0.23 mmol). The reaction was stirred for 1 h and then the volatiles were removed. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 22 mg (19%) of the title compound as a white powder. LRMS (ES+): 510.2 $(M+H)^+$.

EXAMPLE 146

1-[(4-Methoxy)phenyl]-3-[(3-hydroxypropyl)carboxyamide]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl) carboxyamide

[0287] To a solution of 1-[(4-methoxy)phenyl]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide-3-carboxylic acid (100 mg, 0.23 mmol) in 5 mL of acetonitrile was added triethylamine (0.064 mL, 0.46 mmol) and *iso*-butyl chloroformate (0.030 mL, 0.23 mmol). After stirring at ambient temperature for 30 min, there was added 3-hydroxypropylamine (0.02 mL, 0.23 mmol). The reaction was stirred for 1 h and then the volatiles were removed. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 38 mg (30%) of the title compound as a white powder. LRMS (ES+): 492.3 $(M+H)^+$.

EXAMPLE 147

1-[(4-Methoxy)phenyl]-3-[methylcarboxyamide]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl) carboxyamide

[0288] To a solution of 1-[(4-methoxy)phenyl]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide-3-carboxylic acid (100 mg, 0.23 mmol) in 5 mL of acetonitrile was added triethylamine (0.096 mL, 0.69 mmol) and *iso*-butyl chloroformate (0.033 mL, 0.25 mmol). After stirring at ambient temperature for 30 min, there was added methylamine hydrochloride (23 mg, 0.35 mmol). The reaction was stirred for 1 h and then the volatiles were removed. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 15 mg (15%) of the title compound as a white powder. LRMS (ES+): 448.2 $(M+H)^+$.

EXAMPLE 148

1-[(4-Methoxy)phenyl]-3-[(benzyl)carboxyamide]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl) carboxyamide

[0289] To a solution of 1-[(4-methoxy)phenyl]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide-3-carboxylic acid (100 mg, 0.23 mmol) in 5 mL of acetonitrile was added triethylamine (0.096 mL, 0.69 mmol) and *iso*-butyl chloroformate (0.033 mL, 0.25 mmol). After stirring at ambient temperature for 30 min, there was added benzylamine hydrochloride (49 mg, 0.35 mmol). The reaction was stirred for 1 h and then the volatiles were removed. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 19 mg (16%) of the title compound as a white powder. LRMS (ES+): 524.2 $(M+H)^+$.

EXAMPLE 149

1-[(4-Methoxy)phenyl]-3-[(dimethyl)carboxyamide]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl) carboxyamide

[0290] To a solution of 1-[(4-methoxy)phenyl]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide-3-carboxylic acid (100 mg, 0.23 mmol) in 5 mL of acetonitrile was added triethylamine (0.096 mL, 0.69 mmol) and *iso*-butyl chloroformate (0.033 mL, 0.25 mmol). After stirring at ambient temperature for 30 min, there was added aqueous dimethylamine (0.040 mL of a 40% aqueous solution, 0.80 mmol). The reaction was stirred for 1 h and then the volatiles were removed. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 20 mg (19%) of the title compound as a white powder. LRMS (ES+): 462.2 $(M+H)^+$.

EXAMPLE 150

1-[(4-Methoxy)phenyl]-3-[(phenylethyl)carboxyamide]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl) carboxyamide

[0291] To a solution of 1-[(4-methoxy)phenyl]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide-3-carboxylic acid (100 mg, 0.23 mmol) in 5 mL of acetonitrile was added triethylamine (0.096 mL, 0.69 mmol) and *iso*-butyl chloroformate (0.033 mL, 0.25 mmol). After stirring at ambient temperature for 30 min, there was added phenethylamine (0.043 mL, 0.80 mmol). The reaction was stirred for 1 h and then the volatiles were removed. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 15 mg (12%) of the title compound as a white powder. LRMS (ES+): 538.2 $(M+H)^+$.

EXAMPLE 151

1-[(4-Methoxy)phenyl]-3-[(2-hydroxyphenyl)carboxyamide]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl) carboxyamide

[0292] To a solution of 1-[(4-methoxy)phenyl]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide-3-carboxylic acid (100 mg, 0.23 mmol) in 5 mL of acetonitrile was added triethylamine (0.096 mL, 0.69 mmol) and *iso*-butyl chloroformate (0.033 mL, 0.25 mmol). After stirring at ambient temperature for 30 min, there was added 2-hydroxyaniline (75 mg, 0.69 mmol). The reaction was stirred for 1 h and then the volatiles were removed. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 10 mg (8%) of the title compound as a white powder. LRMS (ES+): 526.1 $(M+H)^+$.

EXAMPLE 152

1-[(4-Methoxy)phenyl]-3-[(3-hydroxyphenyl)carboxyamide]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl) carboxyamide

[0293] To a solution of 1-[(4-methoxy)phenyl]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide-3-carboxylic acid (100 mg, 0.23 mmol) in 5 mL of acetonitrile was added triethylamine (0.096 mL, 0.69 mmol) and *iso*-butyl chloroformate (0.033 mL, 0.25 mmol). After stirring at ambient temperature for 30 min, there was added 3-hydroxyaniline (75 mg, 0.69 mmol). The reaction was stirred for 1 h and then the volatiles were removed. The residue was

purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 12 mg (10%) of the title compound as a white powder. LRMS (ES+): 526.2 $(M+H)^+$.

EXAMPLE 153

1-[(4-Methoxy)phenyl]-3-[(4-hydroxyphenyl)carboxyamide]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl) carboxyamide

[0294] To a solution of 1-[(4-methoxy)phenyl]-1H-pyrazole-5-[(4-(*N*-pyrrolidinocarbonyl)phenyl)carboxyamide-3-carboxylic acid (100 mg, 0.23 mmol) in 5 mL of acetonitrile was added triethylamine (0.096 mL, 0.69 mmol) and *iso*-butyl chloroformate (0.033 mL, 0.25 mmol). After stirring at ambient temperature for 30 min, there was added 4-hydroxyaniline (75 mg, 0.69 mmol). The reaction was stirred for 1 h and then the volatiles were removed. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 12 mg (10%) of the title compound as a white powder. LRMS (ES+): 548.1 $(M+Na)^+$.

EXAMPLE 154

1-[(4-Methoxy)phenyl]-3-[(methoxycarbonyl)amino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide

[0295] 1-[(4-Methoxy)phenyl]-3-[(methoxycarbonyl)amino]-5-(methoxycarbonyl)pyrazole. To a solution of 1-[(4-methoxy)phenyl]-5-(methoxycarbonyl)pyrazole-3-carboxylic acid (3.0 g, 10.9 mmol) in 50 mL of acetone at 0°C was added triethylamine (1.66 mL, 11.9 mmol) followed by *iso*-butyl chloroformate (1.14 mL, 11.9 mmol). The resulting was stirred for 30 min whereupon an aqueous solution of sodium azide (2.82 g, 43.4 mmol) was added. The reaction was stirred at 0°C for 1 h. The reaction was then diluted with ethyl acetate and washed with brine. The organics were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in 50 mL of toluene and stirred at 100°C for 1 h. The volatiles were removed *in vacuo* and the residue was dissolved in methanolic sodium methoxide (5 mL of a 25% solution of sodium methoxide in methanol, 21 mmol) and stirred at ambient temperature for 2 h. The reaction was diluted with ethyl acetate, washed with wtaer and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (elution with 1:1 hexanes/ethyl acetate) to afford 1.1 g (33%) of the title compound as a solid. LRMS (DCI): 306.3 $(M+H)^+$.

[0296] 1-[(4-Methoxy)phenyl]-3-[(methoxycarbonyl)amino]-1H-pyrazole-5-[(2'-*tert*-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxysmide. To a solution of (2'-*tert*-butylaminosulfonyl-[1,1']-biphen-4-yl)amine (0.90 g, 2.95 mmol) in 20 mL of methylene chloride at ambient temperature was added trimethylaluminum (8.85 mL of a 2.0 M solution in toluene, 17.68 mmol) dropwise. The resulting solution was allowed to stir until no more gas evolution was observed (-15 min). To this solution was added 1-[(4-methoxy)phenyl]-3-(methoxycarbonylamino)-5-(methoxycarbonyl)pyrazole (0.90 g, 2.95 mmol) in 10 mL of methylene chloride. The resulting solution was stirred at 40° C for 16 h and then was cooled to ambient temperature and quenched by the addition of saturated aq NH_4Cl. After diluting with ethyl acetate, the organic layer was washed with 10% aq HCl, saturated aq $NaHCO_3$ and brine, dried ($MgSO_4$), filtered through a pad of silica gel and concentrated *in vacuo*. The solid residue was recrystallized from hexanes/ethyl acetate to afford 1.4 g (82%) of the title compound. LRMS (ES+): 577.9 (M+H)+.

[0297] 1-[(4-Methoxy)phenyl]-3-[(methoxycarbonyl)amino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide. A solution of 1-[(4-methoxy)phenyl]-3-[(methoxycarbonyl)amino]-1H-pyrazole-5-[(2'-*tert*-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (0.40 g, 0.69 mmol) in 5 mL of trifluoroacetic acid was stirred at reflux for 20 min and then was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 200 mg (56%) of the title compound as a white powder. LRMS (ES+): 521.8 (M+H)+.

EXAMPLE 155

1-[(4-Methoxy)phenyl]-3-amino-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0298] To a solution of 1-[(4-methoxy)phenyl]-3-[(methoxycarbonyl)amino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (0.22 g, 0.42 mmol) in 10 mL of 1:1 water/methanol was added potassium hydroxide (2.0 g, 35 mmol). The resulting mixture was stirred at 70°C for 4 h and then was cooled to ambient temperature and was acidified with aq HCl. The reaction mixture was diluted with ethyl acetate and the organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 75 mg (38%) of the title compound as a white

powder. LRMS (ES+): 463.8 (M+H)+.

EXAMPLE 156

1-[(4-Methoxy)phenyl]-3-[(methoxycarbonyl)methylamino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0299] To a solution of 1-[(4-methoxy)phenyl]-3-amino-1H-pyrazole-5-[(2'-*tert*-butylaminosulfonyl-[1,1']-biphen-4-yl) carboxyamide (1.0 g, 1.92 mmol) in 10 mL of DMF was added sodium bicarbonate (0.24 g, 2.88 mmol) and methyl bromoacetate (0.22 mL, 2.30 mmol) The resulting mixture was stirred at 85°C for 16 h. The reaction was not complete so additional portions of sodium bicarbonate (0.48 g, 5.76 mmol) and methyl bromoacetate (0.22 mL, 2.30 mmol) were added and the reaction was stirred at 95°C for 6 h longer. The reaction was cooled to ambient temperature and was diluted with ethyl acetate. The organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in 5 mL of trifluoroacetic acid and was stirred at reflux for 20 min and then was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 450 mg (44%) of the title compound as a white powder. LRMS (ES+): 536.0 (M+H)+.

EXAMPLE 157

1-[(4-Methoxy)phenyl]-3-[(2-hydroxy)ethylamino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide

[0300] 1-[(4-Methoxy)phenyl]-3-[*N*-glycyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide. To a solution of 1-[(4-methoxy)phenyl]-3-[(methoxycarbonyl)methylamino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (0.40 g, 0.75 mmol) in 10 mL of 1:1 methanol/water was added lithium hydroxide monohydrate (0.13 g, 2.98 mmol). The resulting mixture was stirred at ambient temperature for 16 h. The reaction was acidified with aq HCl and was diluted with ethyl acetate. The organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 200 mg (51%) of the title compound as a white powder. LRMS (ES+): 522.0 (M+H)+.

[0301] 1-[(4-Methoxy)phenyl]-3-[(2-hydroxy)ethylamino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide. To a solution of 1-[(4-methoxy)phenyl]-3-[*N*-glycyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (0.14 g, 0.27 mmol) in tetrahydrofuran at-20°C was added triethylamine (0.038 mL, 0.27 mmol) and ethyl chloroformate (0.026 mL, 0.27 mmol). This mixture was stirred for 30 min and then there was added sodium borohydride (20 mg, 0.54 mmol) in a minimal amount of water. The reaction mixture was stirred with slow warming to room temperature for 1 h and then was quenched with 10% aq HCl. After diluting with ethyl acetate, the organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 35 mg (26%) of the title compound as a white powder. LRMS (ES+): 507.9 (M+H)+.

EXAMPLE 158

1-[(4-Methoxy)phenyl]-3-[*E*-2-(methoxycarbonyl)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide

[0302] 1-[(4-Methoxy)phenyl]-3-(hydroxymethyl)-1H-pyrazole-5-(methoxycarbonyl)pyrazole. To a solution of 1-[(4-methoxy)phenyl]-1H-pyrazole-5-(methoxycarbonyl)pyrazole-3-carboxylic acid (2.4 g, 8.69 mmol) in 50 mL of tetrahydrofuran at-20°C was added triethylamine (1.21 mL, 8.69 mmol) and ethyl chloroformate (0.83 mL, 8.69 mmol). This mixture was stirred for 30 min and then there was added sodium borohydride (0.66 g, 17.4 mmol) in a minimal amount of water. The reaction mixture was stirred with slow warming to room temperature for 1 h and then was quenched with 10% aq HCl. After diluting with ethyl acetate, the organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (elution with 3:2 ethyl acetate/hexane) to afford 1.4 g (61%) of the title compound. LRMS (DCI): 263.3 (M+H)+.

[0303] 1-[(4-Methoxy)phenyl]-3-(hydroxymethyl)-1H-pyrazole-5-[(2'-*tert*-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxyamide. To a solution of of (2'-*tert*-butylaminosulfonyl-[1,1']-biphen-4-yl)amine (1.44 g, 4.73 mmol) in 40 mL of methylene chloride at ambient temperature was added trimethylaluminum (14.2 mL of a 2.0 M solution in toluene, 28.4 mmol) dropwise. The resulting solution was allowed to stir until no more gas evolution was observed (- 15 min).

To this solution was added 1-[(4-methoxy)phenyl]-3-(hydroxymethyl)-5-(methoxycarbonyl)pyrazole (1.24 g, 4.73 mmol) in 10 mL of methylene chloride. The resulting solution was stirred at 40° C for 16 h and then was cooled to ambient temperature and quenched by the addition of saturated aq NH_4Cl. After diluting with ethyl acetate, the organic layer was washed with 10% aq HCl, saturated aq $NaHCO_3$ and brine, dried ($MgSO_4$), filtered through a pad of silica gel and concentrated *in vacuo*. The solid residue was recrystallized from hexanes/ethyl acetate to afford 1.7 g (68%) of the title compound. LRMS (ES+): 557.1 $(M+Na)^+$.

[0304] 1-[(4-Methoxy)phenyl]-3-(carboxaldehyde)-1H-pyrazole-5-[(2'-*tert*-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxyamide. To a solution of oxalyl chloride (0.33 mL, 3.81 mmol) in 20 mL of methylene chloride at-78°C was added dimethyl sulfoxide (0.54 mL, 7.63 mmol). This mixture was stirred for 15 minutes and then 1-[(4-methoxy)phenyl]-3-(hydroxymethyl)-1H-pyrazole-5-[(2'-*tert*-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (1.70 g, 3.18 mmol) was added in 10 mL of methylene chloride. The reaction was allowed to stir while slowly warming to room temperature over 2 h. Triethylamine (2.21 mL, 15.90 mmol) was added and the reaction was stirred at room temperature for 30 min. The reaction was diluted with ethyl acetate and the organic layer was washed with 10% HCl, sat'd aq $NaHCO_3$ and brine, dried ($MgSO_4$), filtered through a pad of silica gel and concentrated *in vacuo* to afford 1.3 g (76%) of the title compound which was sufficiently pure to be used without purification. LRMS (ES+): 533.2 $(M+H)^+$.

[0305] 1-[(4-Methoxy)phenyl]-3-[*E*-2-(methoxycarbonyl)ethenyl]-1H-pyrazole-5-[(2'-*tert*-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxyamide. To a solution of 1-[(4-methoxy)phenyl]-3-(carboxaldehyde)-1H-pyrazole-5-[(2'-*tert*-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (1.30 g, 2.44 mmol) in 30 mL of methylene chloride was added methyl (triphenylphosphoranylidene)acetate (0.98 g, 2.92 mmol). The mixture was allowed to stir at ambient temperature for 18 h. The volatiles were removed *in vacuo* and the residue was purified by flash chromatography (elution with 1:1 ethyl acetate/hexane) to afford 1.2 g (83%) of the title compound. LRMS (ES+): 589.1 $(M+H)^+$.

[0306] 1-[(4-Methoxy)phenyl]-3-[*E*-2-(methoxycarbonyl)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide. A solution of 1-[(4-methoxy)phenyl]-3-[*E*-2-(methoxycarbonyl)ethenyl]-1H-pyrazole-5-[(2'-*tert*-butylaminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (1.2 g, 2.04 mmol) in 10 mL of trifluoroacetic acid was stirred at reflux for 20 min and then was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 1.0 g (90%) of the title compound as a white powder. LRMS (ES+): 533.0 $(M+H)^+$.

EXAMPLE 159

1-[(4-Methoxy)phenyl]-3-[2-(methoxycarbonyl)ethyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide

[0307] To a solution of 1-[(4-methoxy)phenyl]-3-[*E*-2-(methoxycarbonyl)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (35 mg, 0.065 mmol) in 20 mL of absolute ethanol at ambient temperature was added 10% palladium on carbon catalyst (3.5 mg). This mixture was stirred under 1 atm of hydrogen gas for 3 h and then was filtered through a pad of celite and concentrated *in vacuo*. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 15 mg (42%) of the title compound as a white powder. LRMS (ES+): 534.9 $(M+H)^+$.

EXAMPLE 160

1-[(4-Methoxy)phenyl]-3-[*E*-2-(carboxy)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide

[0308] To a solution of 1-[(4-methoxy)phenyl]-3-[*E*-2-(methoxycarbonyl)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (1.2 g, 2.25 mmol) in 20 mL of 1:1 methanol/water at ambient temperature was lithium hydroxide monohydrate (0.19 g, 4.5 mmol). This mixture was stirred for 3 h and then was acidified with aq HCl and diluted with ethyl acetate. The organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 1.0 g (83%) of the title compound as a white powder. LRMS (ES-): 516.8 $(M-H)^-$.

EXAMPLE 161

1-[(4-Methoxy)phenyl]-3-[2-(carboxy)ethyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0309] To a solution of 1-[(4-methoxy)phenyl]-3-[*E*-2-(carboxy)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (40 mg, 0.077 mmol) in 20 mL of absolute ethanol at ambient temperature was added 10%

palladium on carbon catalyst (20 mg). This mixture was stirred under 1 atm of hydrogen gas for 3 h and then was filtered through a pad of celite and concentrated *in vacuo*. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 10 mg (25%) of the title compound as a white powder. LRMS (ES+): 520.9 $(M+H)^+$.

EXAMPLE 162

1-[(4-Methoxy)phenyl]-3-[*E*-2-(carboxyamide)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide

[0310] To a solution of 1-[(4-methoxy)phenyl]-3-[*E*-2-(carboxy)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (140 mg, 0.27 mmol) in 10 mL of acetonitrile was added triethylamine (0.11 mL, 0.81 mmol) and *iso*-butyl chloroformate (0.039 mL, 0.30 mmol). After stirring at ambient temperature for 30 min, there was added methanolic ammonia solution (0.27 mL of a 2.0 M solution of ammonia in methanol, 0.54 mmol). The reaction was stirred for 16 h and then the volatiles were removed. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 35 mg (25%) of the title compound as a white powder. LRMS (ES+): 517.9 $(M+H)^+$.

EXAMPLE 163

1-[(4-Methoxy)phenyl]-3-[*E*-2-(hydroxymethyl)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide

[0311] To a solution of 1-[(4-methoxy)phenyl]-3-[*E*-2-(carboxy)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (1.0 g, 1.93 mmol) in 20 mL of tetrahydrofuran at-20°C was added triethylamine (0.27 mL, 1.93 mmol) and *iso*-butyl chloroformate (0.25 mL, 1.93 mmol). This mixture was stirred for 30 min and then there was added sodium borohydride (0.22 g, 5.78 mmol) in a minimal amount of water. The reaction mixture was stirred with slow warming to room temperature for 1 h and then was quenched with 10% aq HCl. After diluting with ethyl acetate, the organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 0.5 g (52%) of the title compound as a white powder. LRMS (ES+): 504.9 $(M+H)^+$.

EXAMPLE 164

1-[(4-Methoxy)phenyl]-3-(3-hydroxypropyl)-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

AND EXAMPLE 165

1-[(4-Methoxy)phenyl]-3-propyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide

[0312] To a solution of 1-[(4-methoxy)phenyl]-3-[*E*-2-(hydroxymethyl)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide (40 mg, 0.08 mmol) in 20 mL methanol at ambient temperature was added 10% palladium on carbon catalyst (4 mg). This mixture was stirred under 1 atm of hydrogen gas for 3 h and then was filtered through a pad of celite and concentrated in *vacuo*. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 15 mg (38%) of EXAMPLE 164 as a white powder. LRMS (ES+) : 506.9 $(M+H)^+$. There was also obtained 8 mg (20%) of EXAMPLE 165 as a white powder. LRMS (ES+): 490.9 $(M+H)^+$.

EXAMPLE 166

1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-cyano-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide

[0313] 1-[(4-Mothoxy)phenyl]-3-(trifluoromethyl)-4-cyano-1H-pyrazole-5-(2-furyl)pyrazole. To a solution of 2-furoylacetonitrile (0.91 g, 6.73 mmol) in 20 mL of absolute ethanol was added sodium ethoxide (2.5 mL of a 21% weight solution in ethanol, 6.73 mmol) followed by 2, 2, 2-trifluoroacetoyl bromide-N-(4-methoxyphenyl)hydrazone (2.0 g, 6.73 mmol). This mixture was stirred at ambient temperature for 4 h. The volatiles were removed *in vacuo* and the residue was dissolved in ethyl acetate, washed with water and brine, dried ($MgSO_4$) and concentrated. The residue

was purified by recrystallization from hexane/ethyl acetate to afford 1.1 g (49%) of the title compound.

[0314] 1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-cyano-pyrazole-5-carboxylic acid. To a solution of 1-[(4-methoxy)phenyl]-3-(trifluoromethyl)-4-cyano-5-(2-furyl)pyrazole (0.68 g, 2.04 mmol) in 4:4:6 carbon tetrachloride/acetonitrile/water was added sodium periodate (1.96 g, 9.2 mmol) and ruthenium (III) chloride monohydrate (42 mg, 0.20 mmol). The resulting biphasic reaction was stirred vigorously at ambient temperature for 24 h. The reaction was quenched with 10% aq HCl and diluted with ethyl acetate. The organics were washed with brine, dried ($MgSO_4$), filtered through a pad of Celite and concentrated. The residue was dissolved in 1:1 hexanes/ethyl acetate and extracted with sat'd aq Na_2CO_3 (2 times). The combined aqueous extracts were acidified and extracted with ethyl acetate. The ethyl acetate extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford 0.42 g (67%) of the title compound as a solid. LRMS (ES-): 310.0 $(M-H)^-$.

[0315] 1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-cyano-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide. To a solution of 1-[(4-methoxy)phenyl]-3-(trifluoromethyl)-4-cyanopyrazole-5-carboxylic acid (0.41 g, 1.32 mmol) in 20 mL of methylene chloride was added oxalyl chloride (0.17 mL, 1.98 mmol) and 2 drops of dimethylformamide. The reaction was stirred at ambient temperature for 6 h and then the volatiles were removed in *vacuo*. The residue was dissolved in 20 mL of methylene chloride and then there was added 4-dimethylaminopyridine (0.48 g, 3.96 mmol). The reaction was stirred for 10 min and then there was added (2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)amine hydrochloride (0.47 g, 1.45 mmol). The resulting mixture was allowed to stir at ambient temperature for 16 h. The reaction was diluted with ethyl acetate and the organics were washed with 10% aq HCl, sat'd aq $NaHCO_3$ and brine, dried ($MgSO_4$), filtered through a pad of silica gel and concentrated to afford 0.6 g (81%) of the title compound as a tan solid. LRMS (ES+): 581.3 $(M+Na)^+$.

EXAMPLE 167

1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-(amidino)-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide

AND EXAMPLE 168

1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-(*N*-hydroxyamidino)-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide

[0316] To a solution of 1-[(4-methoxy)phenyl]-3-(trifluoromethyl)-4-cyano-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide (100 mg, 0.18 mmol) in 5 mL of absolute ethanol was added hydroxylamine hydrochloride (38 mg, 0.54 mmol) and sodium carbonate (29 mg, 0.27 mmol). This mixture was stirred at 80°C for 16 h. The reaction was diluted with water and ethyl acetate. The organics were washed with brine, dried ($MgSO_4$) and concentrated to a solid. The residue was dissolved in 10 mL of absolute ethanol and then there was added cyclohexene (1 mL), 20% palladium hydroxide on carbon (50 mg) and acetic acid (0.02 mL, 0.36 mmol). The resulting mixture was stirred at 80°C for 6 h. The reaction was allowed to cool and was filtered through a pad of celite and concentrated *in vacuo*. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 20 mg (16%) of EXAMPLE 167 as a white powder. LRMS (ES+): 576.2 $(M+H)^+$. There was also obtained 15 mg (12%) of EXAMPLE 168 as a white powder. LRMS (ES+): 592.2 $(M+H)^+$.

EXAMPLE 169

1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-(ethoxycarbonyl)-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide

[0317] 1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-(ethoxycarbonyl)-5-(2-furyl)pyrazole. To a solution of ethyl 3-(2-furyl)-3-ketopropionate (2.45 g, 13.4 mmol) in 20 mL of absolute ethanol was added sodium ethoxide (4.6 mL of a 21% weight solution in ethanol, 12.2 mmol) followed by 2, 2, 2-trifluoroacetoyl bromide-N-(4-methoxyphenyl)hydrazone (1.82 g, 6.1 mmol). This mixture was stirred at ambient temperature for 4 h. The volatiles were removed *in vacuo* and the residue was dissolved in ethyl acetate, washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was purified by recrystallization from hexane/ethyl acetate to afford 1.4 g (61%) of the title compound. LRMS (ES+): 381.2 $(M+H)^+$.

[0318] 1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-(ethoxycarbonyl)-pyrazole-5-carboxylic acid. To a solution of 1-[(4-methoxy)phenyl]-3-(trifluoromethyl)-4-(ethoxycarbonyl)-5-(2-furyl)pyrazole (1.0 g, 2.63 mmol) in 4:4:6 carbon tetrachloride/acetonitrile/water was added sodium periodate (2.5 g, 11.8 mmol) and ruthenium (III) chloride monohydrate (11 mg, 0.05 mmol). The resulting biphasic reaction was stirred vigorously at ambient temperature for 24 h. The

reaction was quenched with 10% aq HCl and diluted with ethyl acetate. The organics were washed with brine, dried ($MgSO_4$), filtered through a pad of Celite and concentrated. The residue was dissolved in 1:1 hexanes/ethyl acetate and extracted with sat'd aq Na_2CO_3 (2 times). The combined aqueous extracts were acidified and extracted with ethyl acetate. The ethyl acetate extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford 0.5 g (53%) of the title compound as a solid. LRMS (ES-): 357.0 $(M-H)^-$.

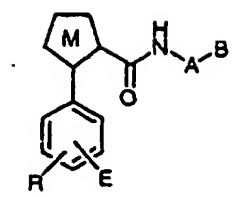
[0319] 1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-(ethoxycarbonyl)-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide. To a solution of 1-[(4-methoxy)phenyl]-3-(trifluoromethyl)-4-(ethoxycarbonyl)-pyrazole-5-carboxylic acid (0.5 g, 1.4 mmol) in 10 mL of methylene chloride was added oxalyl chloride (0.18 mL, 2.1 mmol) and 2 drops of dimethylformamide. The reaction was stirred at ambient temperature for 6 h and then the volatiles were removed *in vacuo*. The residue was dissolved in 20 mL of methylene chloride and then there was added 4-dimethylaminopyridine (0.51 g, 4.2 mmol). The reaction was stirred for 10 min and then there was added (2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)amine hydrochloride (0.42 g, 1.4 mmol). The resulting mixture was allowed to stir at ambient temperature for 16 h. The reaction was diluted with ethyl acetate and the organics were washed with 10% aq HCl, sat'd aq $NaHCO_3$ and brine, dried ($MgSO_4$), filtered through a pad of silica gel and concentrated to afford 0.6 g (70%) of the compound of EXAMPLE 169 as a solid. A portion was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford the title compound as a white powder. LRMS (ES+): 628.1 $(M+Na)^+$.

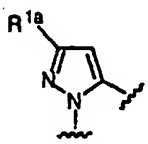
EXAMPLE 170

1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl) carboxyamide-4-carboxylic acid

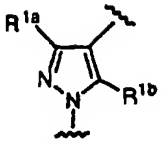
[0320] To a solution of 1-[(4-methoxy)phenyl]-3-(trifluoromethyl)-4-(ethoxycarbonyl)-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide (0.30 g, 0.49 mmol) in 10 mL of 1:1 methanol/water was added potassium hydroxide (55 mg, 0.98 mmol). The reaction was stirred at 60°C for 2 h and then was cooled to room temperature and acidified with 10% aq HCl. The mixture was diluted with ethyl acetate, washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by prep HPLC (C18 reverse phase column, elution with a H_2O/CH_3CN gradient with 0.5% TFA) and lyophilized to afford 150 mg (53 %) of the title compound as a white powder. LRMS (ES-): 576.2 $(M-H)^-$.

Table 1

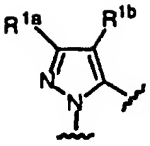




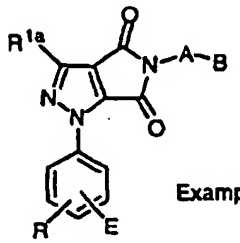
Core-A



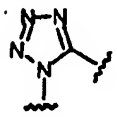
Core-B



Core-C



Example 73



Core-D

Ex	R,E	M	R^{1a}	A-B
2	2-CH_3O	Core-A	CH_3	2'-H_2NSO_2-biphen-4-yl
3	3-CH_3O	Core-A	CH_3	2'-H_2NSO_2-biphen-4-yl
4	4-CH_3O	Core-A	CH_3	2'-H_2NSO_2-biphen-4-yl
5	2-HO	Core-A	CH_3	2'-H_2NSO_2-biphen-4-yl
6	3-HO	Core-A	CH_3	2'-H_2NSO_2-biphen-4-yl
7	4-HO	Core-A	CH_3	2'-H_2NSO_2-biphen-4-yl
8	4-CH_3O	Core-A	CH_3	2'-H_2NSO_2-3-F-biphen-4-yl
9	4-CH_3O	Core-A	CH_3	2'-H_2NSO_2-3-Br-biphen-4-yl
10	4-CH_3O	Core-A	CH_3	2'-H_2NSO_2-3-I-biphen-4-yl
11	4-CH_3O	Core-A	CH_3	2'-H_2NSO_2-3-methylbiphen-4-yl
12	4-CH_3O	Core-A	CH_3	4-$(CH_3)_2NC(O))C_6H_4$
13	4-CH_3O	Core-A	CH_3	4-(N-pyrrolidinocarbonyl)C_6H_4
14	4-CH_3O	Core-A	CH_3	4-(N-pyrrolidinomethyl)C_6H_4
15	4-CH_3O	Core-A	CF_3	2'-H_2NSO_2-biphen-4-yl
16	4-CH_3O	Core-A	CF_3	4-(N-pyrrolidinocarbonyl)C_6H_4
17	4-CH_3O	Core-A	CF_3	5-(2'-CH_3SO_2-C_6H_4)pyrid-2-yl
18	4-CH_3O	Core-A	CF_3	5-(N-pyrrolidinocarbonyl)pyrid-2-yl
19	4-CH_3O	Core-A	CH_3	5-(N-pyrrolidinocarbonyl)pyrid-2-yl
20	4-CH_3O	Core-A	CH_3	5-(2'-H_2NSO_2-C_6H_4)pyrid-2-yl
21	4-CH_3O	Core-A	CH_3	4-(3'-HO-N-pyrrolidinocarbonyl)C_6H_4

37	4-CH_3O	Core-D	-	2'-H_2NSO_2-biphen-4-yl
38	4-CH_3O 3-Cl	Core-A	CH_3	2'-H_2NSO_2-biphen-4-yl
39	4-CF_3O	Core-A	CH_3	2'-H_2NSO_2-biphen-4-yl
40	3-Br	Core-A	CH_3	2'-H_2NSO_2-biphen-4-yl
41	3-I	Core-A	CH_3	2'-H_2NSO_2-biphen-4-yl
42	3,4-OCH_2O	Core-A	CH_3	2'-H_2NSO_2-biphen-4-yl
43	4-CH_3O	Core-A	CH_2OH	4-(N-pyrrolidinocarbonyl)C_6H_4
44	4-CH_3O	Core-A	CHO	4-(N-pyrrolidinocarbonyl)C_6H_4
45	4-CH_3O	Core-A	CO_2H	4-(N-pyrrolidinocarbonyl)C_6H_4
46	4-CH_3O	Core-A	CO_2CH_3	4-(N-pyrrolidinocarbonyl)C_6H_4
47	4-Cl	Core-A	CH_3	2'-H_2NSO_2-biphen-4-yl
48	4-Cl	Core-A	CH_3	5-(2'-H_2NSO_2-C_6H_4)pyrid-2-yl
49	3,4-dicl)	Core-A	CH_3	2'-H_2NSO_2-biphen-4-yl
50	3-Cl	Core-A	CH_3	2'-H_2NSO_2-biphen-4-yl

57	4-CH_3O	Core-A	CH_3S	2'-H_2NSO_2-biphen-4-yl
58	4-CH_3O	Core-A	CH_3SO_2	5-(2'-CH_3CO_2-C_6H_4)pyrimid-2-yl
59	4-CH_3O	Core-A	CH_3SO_2	2'-H_2NSO_2-biphen-4-yl
60	4-CH_3O	Core-A	CH_3S	4-(N-pyrrolidinocarbonyl)C_6H_4
61	4-CH_3O	Core-A	CH_3S	2'-CH_3SO_2-biphen-4-yl
62	4-CH_3O	Core-A	CH_3SO_2	4-(N-pyrrolidionocarbonyl)C_6H_4
63	4-CH_3O	Core-A	CH_3OCH_2	2'-H_2NSO_2-biphen-4-yl
64	4-CH_3O	Core-A	$CH_3OC(O)$	2'-H_2NSO_2-biphen-4-yl
65	4-CH_3O	Core-A	$CH_3SO_2CH_2$	2'-H_2NSO_2-biphen-4-yl
66	4-CH_3O	Core-A	CF_3	5-(2'-CH_3SO_2-C_6H_4)pyrimid-2-yl
67	4-CH_3O	Core-A	CH_3	4-(2'-CH_3CO_2-pyrrolidinocarbonyl)C_6H_4
68	4-CH_3O	Core-A	CF_3	4-(3'-H_2N-pyrrolidinocarbonyl)C_6H_4
69	4-CH_3O	Core-A	CH_3	4-(3'-CH_3O-pyrrolidinocarbonyl)C_6H_4
70	4-CH_3O	Core-A	CF_3	5-(2'-H_2NSO_2-C_6H_4)pyrid-2-yl
71	4-CH_3O	Core-A	CF_3	4-amidinophenyl
72	4-CH_3O	Core-A	CF_3	4-(N-pyrrolidino-C(=NH))C_6H_4
73	4-CH_3O	-	CF_3	2'-H_2NSO_2-biphen-4-yl
74	4-CH_3O	Core-B	3-CF_3, 5-CO_2CH_3	2'-H_2NSO_2-biphen-4-yl
75	4-CH_3O	Core-B	3-CF_3, 5-$(CH_2)_2OH$	2'-H_2NSO_2-biphen-4-yl
76	4-CH_3O	Core-A	CF_3	4-(N-pyrrolidino-C(=NH))C_6H_4
77	4-CH_3O	Core-A	CF_3	4-(N-pyrrolidino-C(=NCO_2-i-butyl))C_6H_4
78	4-CH_3O	Core-A	CF_3	4-(N-pyrrolidino-C(=N)SO_2CH_3)C_6H_4
79	4-CH_3O	Core-A	CF_3	4-amidinophenylmethyl
80	4-CH_3O	Core-A	CF_3	4-(N-pyrrolidino-C(=NH_2))C_6H_4-CH_2-
81	4-CH_3O	Core-A	CF_3	N-benzyl-piperidin-4-yl
82	4-CH_3O	Core-A	CF_3	N-(pyrid-2-lymethyl)piperidin-4-yl
83	4-CH_3O	Core-A	CF_3	4-(2'-methylimidazolyl)C_6H_4
84	4-CH_3O	Core-A	CH_3	4-(5'-methylimidazolyl)C_6H_4
85	4-CH_3O	Core-A	CH_3	4-(4'-methylimidazolyl)C_6H_4
86	4-CH_3O	Core-A	CF_3	4-(5'-$CH_3C(O)$-imidazolyl)C_6H_4
87	4-CH_3O	Core-A	CF_3	4-(5'-carboxyimidazolyl)C_6H_4
88	4-CH_3O	Core-A	CF_3	4-(5'-$CH_3NHC(O)$-imidazolyl)C_6H_4
89	4-CH_3O	Core-A	CF_3	4-(5'-$H_2NC(O)$-imidazolyl)C_6H_4
90	4-CH_3O	Core-A	CF_3	4-(5'-$CH_3NHC(O)$-imidazolyl)C_6H_4
91	4-CH_3O	Core-A	CH_2OH	4-(N-pyrrolidinocarbonyl)C_6H_4
92	4-CH_3O	Core-A	CHO	4-(N-pyrrolidinocarbonyl)C_6H_4

93	4-CH_3O	Core-A	CO_2H	4-(N-pyrrolidinocarbonyl)C_6H_4
94	4-CH_3O	Core-A	CO_2CH_3	4-(N-pyrrolidinocarbonyl)C_6H_4
95	4-CH_3O	Core-A	CH_2CN	4-(N-pyrrolidinocarbonyl)C_6H_4
96	4-CH_3O	Core-A	CH_2CO_2H	4-(N-pyrrolidinocarbonyl)C_6H_4
97	4-CH_3O	Core-A	CH_2Br	2'-H_2NSO_2-biphen-4-yl
98	4-CH_3O	Core-A	CH_2NH_2	2'-H_2NSO_2-biphen-4-yl
99	4-CH_3O	Core-A	CH_2NH_2-SO_2CH_3	2'-H_2NSO_2-biphen-4-yl
100	4-CH_3O	Core-A	CH_2-imidazole	2'-H_2NSO_2-biphen-4-yl
101	4-CH_3O	Core-A	CH_2OH	2'-H_2NSO_2-biphen-4-yl
102	4-CH_3O	Core-A	CH_2-$OC(O)CF_3$	2'-H_2NSO_2-biphen-4-yl
103	4-CH_3O 2-CO_2Me	Core-A	CF_3	2'-CH_3SO_2-biphen-4-yl
104	4-CH_3O 2-CO_2H	Core-A	CF_3	2'-CH_3SO_2-biphen-4-yl
105	4-CH_3O 2-CO_2CH_3	Core-A	CF_3	2'-H_2NSO_2-biphen-4-yl
106	4-CH_3O 2-CO_2H	Core-A	CF_3	2'-t-Bu-$HNSO_2$-biphen-4-yl
107	4-CH_3O 2-CO_2H	Core-A	CF_3	2'-H_2NSO_2-biphen-4-yl
108	4-CH_3O 2-CH_2OH	Core-A	CF_3	2'-H_2NSO_2-biphen-4-yl
109	4-CH_3O	Core-A	CH_3	4-sec-butyl-phenyl
110	4-CH_3O	Core-A	CH_3	4-(3'-methyl-3'-pyrazolin-5'-on-2'-yl)C_6H_4
111	4-CH_3O	Core-A	CH_3	4-(6'methylbenzothiazol-2'-yl)C_6H_4
112	4-CH_3O	Core-A	CH_3	3,4-dibromophenyl
113	4-CH_3O	Core-A	CH_3	4-butylphenyl
114	4-CH_3O	Core-A	CH_3	4-(4-methylpiperidinyl)C_6H_4
115	4-CH_3O	Core-A	CH_3	4-(2'-methylimidazolyl)C_6H_4
116	4-CH_3O	Core-A	CF_3	4-(N-methylimidazol-2-yl-carbonyl)C_6H_4
117	4-CH_3O	Core-A	CF_3	4-(imidazol-2-yl-hydroxymethyl)C_6H_4
118	4-CH_3O	Core-A	CF_3	4-(N-benzylimidazol-2-yl-hydroxymethyl)C_6H_4
119	4-CH_3O	Core-A	CF_3	4-(imidazol-2-yl-carbonyl)C_6H_4

120	4-CH_3O	Core-A	CF_3	[(thiazol-2-yl)(4'-$CH_3OC_6H_4$-NH)CH_2]C_6H_4
121	4-CH_3O	Core-A	CF_3	4-(2'thiazolin-2'yl-carbonyl)C_6H_4
122	4-CH_3O	Core-A	CF_3	4-(2'-imidazolin-2'yl)C_6H_4
123	4-CH_3O	Core-A	CF_3	4-($H_2N(CH_2)_2NHC(O)$)C_6H_4
124	4-CH_3O	Core-A	CF_3	4-(1',4',5',6'-tetrahydropyrimid-2-yl)C_6H_4
125	4-CH_3O	Core-A	CF_3	4-(N-methyl-1',4',5',6'-tetrahydropyrimid-2-yl)C_6H_4
126	4-CH_3O	Core-A	CF_3	4-(1',4',5',6'-tetrahydropyrimid-2-yl)-2-F-C_6H_4
127	4-CH_3O	Core-A	CF_3	4-(N-CH_3-4'-imidazolin-2'yl)-2-F-C_6H_4
128	4-CH_3O	Core-A	CF_3	4-(N-CH_3-4'-imidazolin-2'-yl)C_6H_4
129	4-CH_3O	Core-A	CF_3	4-(guanidino-carbonyl)C_6H_4
130	4-CH_3O	Core-A	CF_3	4-(pyrimid-2-yl)phenyl

141	4-CH_3O	Core-A	$CO_2C_2H_5$	4-(N-pyrrolidinocarbonyl)C_6H_4
142	4-CH_3O	Core-A	$CONH_2$	4-(N-pyrrolidinocarbonyl)C_6H_4
143	4-CH_3O	Core-A	C(O)NH-$(CH_2)_2OH$	4-(N-pyrrolidinocarbonyl)C_6H_4
144	4-CH_3O	Core-A	CONHOH	4-(N-pyrrolidinocarbonyl)C_6H_4
145	4-CH_3O	Core-A	$CONHC_6H_5$	4-(N-pyrrolidinocarbonyl)C_6H_4
146	4-CH_3O	Core-A	$CONH(CH_2)_3OH$	4-(N-pyrrolidinocarbonyl)C_6H_4
147	4-CH_3O	Core-A	$CONHCH_3$	4-(N-pyrrolidinocarbonyl)C_6H_4
148	4-CH_3O	Core-A	$CONHCH_2C_6H_5$	4-(N-pyrrolidinocarbonyl)C_6H_4

149	4-CH_3O	Core-A	$CON(CH_3)_2$	4-(N-pyrrolidinocarbonyl)C_6H_4
150	4-CH_3O	Core-A	$CONH(CH_2)_2$-C_6H_5	4-(N-pyrrolidinocarbonyl)C_6H_4
151	4-CH_3O	Core-A	CONH-2-OH-C_6H_4	4-(N-pyrrolidinocarbonyl)C_6H_4
152	4-CH_3O	Core-A	CONH-3-OH-C_6H_4	4-(N-pyrrolidinocarbonyl)C_6H_4
153	4-CH_3O	Core-A	CONH-4-OH-C_6H_4	4-(N-pyrrolidinocarbonyl)C_6H_4
154	4-CH_3O	Core-A	$NHCO_2CH_3$	2'-H_2NSO_2-biphen-4-yl
155	4-CH_3O	Core-A	NH_2	2'-H_2NSO_2-biphen-4-yl
156	4-CH_3O	Core-A	$NHCH_2CO_2CH_3$	2'-H_2NSO_2-biphen-4-yl
157	4-CH_3O	Core-A	$NH(CH_2)_2OH$	2'-H_2NSO_2-biphen-4-yl
158	4-CH_3O	Core-A	$CH=CHCO_2CH_3$	2'-H_2NSO_2-biphen-4-yl
159	4-CH_3O	Core-A	$CH_2CH_2CO_2CH_3$	2'-H_2NSO_2-biphen-4-yl
160	4-CH_3O	Core-A	$CH=CHCO_2H$	2'-H_2NSO_2-biphen-4-yl
161	4-CH_3O	Core-A	$CH_2CH_2CO_2H$	2'-H_2NSO_2-biphen-4-yl
162	4-CH_3O	Core-A	$CH=CHCONH_2$	2'-H_2NSO_2-biphen-4-yl
163	4-CH_3O	Core-A	$CH=CHCH_2OH$	2'-H_2NSO_2-biphen-4-yl
164	4-CH_3O	Core-A	$(CH_2)_3OH$	2'-H_2NSO_2-biphen-4-yl
165	4-CH_3O	Core-A	$(CH_2)_2CH_3$	2'-H_2NSO_2-biphen-4-yl
166	4-CH_3O	Core-C	3-CF_3, 4-CN	2'-CH_3SO_2-3-F-biphen-4-yl
167	4-CH_3O	Core-C	3-CF_3, 4-amidino	2'-CH_3SO_2-3-F-biphen-4-yl
168	4-CH_3O	Core-C	3-CF_3, 4-amidino-OH	2'-CH_3SO_2-3-F-biphen-4-yl
169	4-CH_3O	Core-C	3-CF_3, 4-$CO_2C_2H_5$	2'-CH_3SO_2-3-F-biphen-4-yl
170	4-CH_3O	Core-C	3-CF_3, 4-CO_2H	2'-CH_3SO_2-3-F-biphen-4-yl

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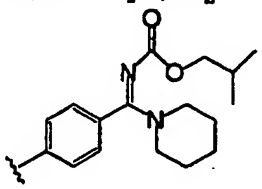
(a)-$CH_2C(O)NHCH_2CO_2CH_3$

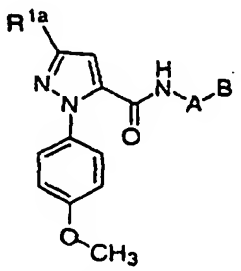
(b)-(1,2,4-triazol-1-yl)CH_2

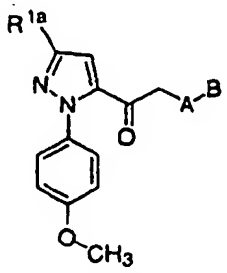
(c)



[0321] The following tables contain representative examples of the present invention. Each entry in each table is intended to be paired with each formulae at the start of the table. For example, example 1 in Table 2 is intended to be paired with each of formulae a_1-f_9.

Table 2





a_1 R^{1a}=CH_3	b_1 R^{1a}=CH_3
a_2 R^{1a}=CF_3	b_2 R^{1a}=CF_3
a_3 R^{1a}=SCH_3	b_3 R^{1a}=SCH_3
a_4 R^{1a}=$SOCH_3$	b_4 R^{1a}=$SOCH_3$
a_5 R^{1a}=SO_2CH_3	b_5 R^{1a}=SO_2CH_3
a_6 R^{1a}=Cl	b_6 R^{1a}=Cl
a_7 R^{1c}=Br	b_7 R^{1a}=Br
a_8 R^{1a}=CO_2CH_3	b_8 R^{1a}=CO_2CH_3
a_9 R^{1a}=CH_2OCH_3	b_9 R^{1a}=CH_2OCH_3

Ex #	A	B
1	phenyl	2-(aminosulfonyl)phenyl
2	phenyl	2-(methylaminosulfonyl)phenyl
3	phenyl	1-pyrrolidinocarbonyl
4	phenyl	2-(methylsulfonyl)phenyl
5	phenyl	4-morpholino
6	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
7	phenyl	4-morpholinocarbonyl
8	2-pyridyl	2-(aminosulfonyl)phenyl
9	2-pyridyl	2-(methylaminosulfonyl)phenyl
10	2-pyridyl	1-pyrrolidinocarbonyl
11	2-pyridyl	2-(methylsulfonyl)phenyl
12	2-pyridyl	4-morpholino
13	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
14	2-pyridyl	4-morpholinocarbonyl
15	3-pyridyl	2-(aminosulfonyl)phenyl
16	3-pyridyl	2-(methylaminosulfonyl)phenyl
17	3-pyridyl	1-pyrrolidinocarbonyl
18	3-pyridyl	2-(methylsulfonyl)phenyl
19	3-pyridyl	4-morpholino
20	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
21	3-pyridyl	4-morpholinocarbonyl
22	2-pyrimidyl	2-(aminosulfonyl)phenyl
23	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
24	2-pyrimidyl	1-pyrrolidinocarbonyl
25	2-pyrimidyl	2-(methylsulfonyl)phenyl
26	2-pyrimidyl	4-morpholino
27	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
28	2-pyrimidyl	4-morpholinocarbonyl
29	5-pyrimidyl	2-(aminosulfonyl)phenyl
30	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
31	5-pyrimidyl	1-pyrrolidinocarbonyl
32	5-pyrimidyl	2-(methylsulfonyl)phenyl
33	5-pyrimidyl	4-morpholino
34	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
35	5-pyrimidyl	4-morpholinocarbonyl
36	2-Cl-phenyl	2-(aminosulfonyl)phenyl
37	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
38	2-Cl-phenyl	1-pyrrolidinocarbonyl
39	2-Cl-phenyl	2-(methylsulfonyl)phenyl
40	2-Cl-phenyl	4-morpholino
41	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
42	2-Cl-phenyl	4-morpholinocarbonyl
43	2-F-phenyl	2-(aminosulfonyl)phenyl
44	2-F-phenyl	2-(methylaminosulfonyl)phenyl
45	2-F-phenyl	1-pyrrolidinocarbonyl
46	2-F-phenyl	2-(methylsulfonyl)phenyl
47	2-F-phenyl	4-morpholino
48	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
49	2-F-phenyl	4-morpholinocarbonyl
50	2,5-diF-phenyl	2-(aminosulfonyl)phenyl
51	2,5-diF-phenyl	2-(methylaminosulfonyl)phenyl
52	2,5-diF-phenyl	1-pyrrolidinocarbonyl
53	2,5-diF-phenyl	2-(methylsulfonyl)phenyl
54	2,5-diF-phenyl	4-morpholino
55	2,5-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl

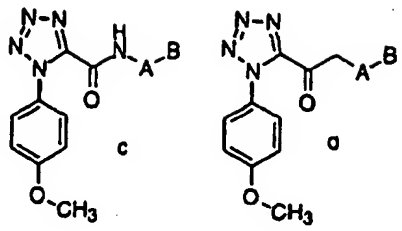
56	2,5-diF-phenyl	4-morpholinocarbonyl
57	phenyl	2-(N-pyrrolidinyl-methyl)phenyl
58	phenyl	2-(N-piperidinyl-methyl)phenyl
59	phenyl	2-(N-morpholino-methyl)phenyl
60	phenyl	2-(N,N'-methylmorpholinium-methyl)phenyl
61	phenyl	2-(N-pyridinium-methyl)phenyl
62	phenyl	2-(N-4-(N,N'-dimethylamino)-pyridinium-methyl)phenyl
63	phenyl	2-(N-azatanyl-methyl)phenyl
64	phenyl	2-(N-azetidinyl-methyl)phenyl
65	phenyl	2-(N-piperazinyl-methyl)phenyl
66	phenyl	2-(N,N'-BOC-piperazinyl-methyl)phenyl
67	phenyl	2-(N-imidazolyl-methyl)phenyl
68	phenyl	2-(N-methoxy-N-methylamino-methyl)phenyl
69	phenyl	2-(N-pyridonyl-methyl)phenyl
70	phenyl	2-(N-(N',N'-dimethylhydrazinyl-methyl)phenyl
71	phenyl	2-(amidinyl)phenyl
72	phenyl	2-(N-guanidinyl)phenyl
73	phenyl	2-(imidazolyl)phenyl
74	phenyl	2-(imidazolidinyl)phenyl
75	phenyl	2-(2-imidazolidinyl-sulfonyl)phenyl
76	phenyl	2-(2-pyrrolidinyl)phenyl
77	phenyl	2-(2-piperidinyl)phenyl
78	phenyl	2-(amidinyl-methyl)phenyl
79	phenyl	2-(2-imidazolidinyl-methyl)phenyl
80	phenyl	2-(N-(2-aminoimidazolyl)-methyl)phenyl
81	phenyl	2-dimethylaminoimidazol-1-yl
82	phenyl	2-(3-aminophenyl)
83	phenyl	2-(3-pyrrolidinylcarbonyl)
84	phenyl	2-glycinoyl
85	phenyl	2-(imidazol-1-ylacetyl)
86	2-pyridyl	2-(N-pyrrolidinyl-methyl)phenyl
87	2-pyridyl	2-(N-piperidinyl-methyl)phenyl
88	2-pyridyl	2-(N-morpholino-methyl)phenyl
89	2-pyridyl	2-(N,N'-methylmorpholinium-methyl)phenyl
90	2-pyridyl	2-(N-pyridinium-methyl)phenyl
91	2-pyridyl	2-(N-4-(N,N'-dimethylamino)-pyridinium-methyl)phenyl
92	2-pyridyl	2-(N-azatanyl-methyl)phenyl
93	2-pyridyl	2-(N-azetidinyl-methyl)phenyl
94	2-pyridyl	2-(N-piperazinyl-methyl)phenyl
95	2-pyridyl	2-(N,N'-BOC-piperazinyl-methyl)phenyl
96	2-pyridyl	2-(N-imidazolyl-methyl)phenyl
97	2-pyridyl	2-(N-methoxy-N-methylamino-methyl)phenyl
98	2-pyridyl	2-(N-pyridonyl-methyl)phenyl
99	2-pyridyl	2-(N-(N',N'-dimethylhydrazinyl-methyl)phenyl
100	2-pyridyl	2-(amidinyl)phenyl
101	2-pyridyl	2-(N-guanidinyl)phenyl
102	2-pyridyl	2-(imidazolyl)phenyl
103	2-pyridyl	2-(imidazolidinyl)phenyl
104	2-pyridyl	2-(2-imidazolidinyl-sulfonyl)phenyl
105	2-pyridyl	2-(2-pyrrolidinyl)phenyl
106	2-pyridyl	2-(2-piperidinyl)phenyl
107	2-pyridyl	2-(amidinyl-methyl)phenyl

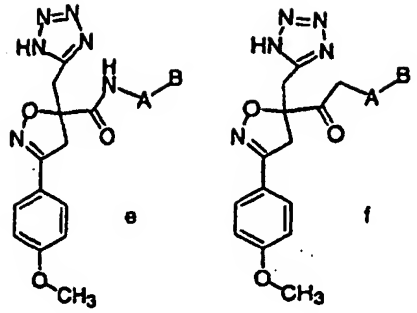
108	2-pyridyl	2-(2-imidazolidinyl-methyl)phenyl
109	2-pyridyl	2-(N-(2-aminoimidazolyl)-methyl)phenyl
110	2-pyridyl	2-dimethylaminoimidazol-1-yl
111	2-pyridyl	2-(3-aminophenyl)
112	2-pyridyl	2-(3-pyrrolidinylcarbonyl)
113	2-pyridyl	2-glycinoyl
114	2-pyridyl	2-(imidazol-1-ylacetyl)
115	3-pyridyl	2-(N-pyrrolidinyl-methyl)phenyl
116	3-pyridyl	2-(N-piperidinyl-methyl)phenyl
117	3-pyridyl	2-(N-morpholino-methyl)phenyl
118	3-pyridyl	2-(N,N'-methylmorpholinium-methyl)phenyl
119	3-pyridyl	2-(N-pyridinium-methyl)phenyl
120	3-pyridyl	2-(N-4-(N,N'-dimethylamino)-pyridinium-methyl)phenyl
121	3-pyridyl	2-(N-azatanyl-methyl)phenyl
122	3-pyridyl	2-(N-azetidinyl-methyl)phenyl
123	3-pyridyl	2-(N-piperazinyl-methyl)phenyl
124	3-pyridyl	2-(N,N'-BOC-piperazinyl-methyl)phenyl
125	3-pyridyl	2-(N-imidazolyl-methyl)phenyl
126	3-pyridyl	2-(N-methoxy-N-methylamino-methyl)phenyl
127	3-pyridyl	2-(N-pyridonyl-methyl)phenyl
128	3-pyridyl	2-(N-(N',N'-dimethylhydrazinyl-methyl)phenyl
129	3-pyridyl	2-(amidinyl)phenyl
130	3-pyridyl	2-(N-guanidinyl)phenyl
131	3-pyridyl	2-(imidazolyl)phenyl
132	3-pyridyl	2-(imidazolidinyl)phenyl
133	3-pyridyl	2-(2-imidazolidinyl-sulfonyl)phenyl
134	3-pyridyl	2-(2-pyrrolidinyl)phenyl
135	3-pyridyl	2-(2-piperidinyl)phenyl
136	3-pyridyl	2-(amidinyl-methyl)phenyl
137	3-pyridyl	2-(2-imidazolidinyl-methyl)phenyl
138	3-pyridyl	2-(N-(2-aminoimidazolyl)-methyl)phenyl
139	3-pyridyl	2-dimethylaminoimidazol-1-yl
140	3-pyridyl	2-(3-aminophenyl)
141	3-pyridyl	2-(3-pyrrolidinylcarbonyl)
142	3-pyridyl	2-glycinoyl
143	3-pyridyl	2-(imidazol-1-ylacetyl)
144	2-pyrimidyl	2-(N-pyrrolidinyl-methyl)phenyl
145	2-pyrimidyl	2-(N-piperidinyl-methyl)phenyl
146	2-pyrimidyl	2-(N-morpholino-methyl)phenyl
147	2-pyrimidyl	2-(N,N'-methylmorpholinium-methyl)phenyl
148	2-pyrimidyl	2-(N-pyridinium-methyl)phenyl
149	2-pyrimidyl	2-(N-4-(N,N'-dimethylamino)-pyridinium-methyl)phenyl
150	2-pyrimidyl	2-(N-azatanyl-methyl)phenyl
151	2-pyrimidyl	2-(N-azetidinyl-methyl)phenyl
152	2-pyrimidyl	2-(N-piperazinyl-methyl)phenyl
153	2-pyrimidyl	2-(N,N'-BOC-piperazinyl-methyl)phenyl
154	2-pyrimidyl	2-(N-imidazolyl-methyl)phenyl
155	2-pyrimidyl	2-(N-methoxy-N-methylamino-methyl)phenyl
156	2-pyrimidyl	2-(N-pyridonyl-methyl)phenyl
157	2-pyrimidyl	2-(N-(N',N'-dimethylhydrazinyl-methyl)phenyl
158	2-pyrimidyl	2-(amidinyl)phenyl
159	2-pyrimidyl	2-(N-guanidinyl)phenyl

160	2-pyrimidyl	2-(imidazolyl)phenyl
161	2-pyrimidyl	2-(imidazolidinyl)phenyl
162	2-pyrimidyl	2-(2-imidazolidinyl-sulfonyl)phenyl
163	2-pyrimidyl	2-(2-pyrrolidinyl)phenyl
164	2-pyrimidyl	2-(2-piperidinyl)phenyl
165	2-pyrimidyl	2-(amidinyl-methyl)phenyl
166	2-pyrimidyl	2-(2-imidazolidinyl-methyl)phenyl
167	2-pyrimidyl	2-(N-(2-aminoimidazolyl)-methyl)phenyl
168	2-pyrimidyl	2-dimethylaminoimidazol-1-yl
169	2-pyrimidyl	2-(3-aminophenyl)
170	2-pyrimidyl	2-(3-pyrrolidinylcarbonyl)
171	2-pyrimidyl	2-glycinoyl
172	2-pyrimidyl	2-(imidazol-1-ylacetyl)
173	2-Cl-phenyl	2-(N-pyrrolidinyl-methyl)phenyl
174	2-Cl-phenyl	2-(N-piperidinyl-methyl)phenyl
175	2-Cl-phenyl	2-(N-morpholino-methyl)phenyl
176	2-Cl-phenyl	2-(N,N'-methylmorpholinium-methyl)phenyl
177	2-Cl-phenyl	2-(N-pyridinium-methyl)phenyl
178	2-Cl-phenyl	2-(N-4-(N,N'-dimethylamino)-pyridinium-methyl)phenyl
179	2-Cl-phenyl	2-(N-azatanyl-methyl)phenyl
180	2-Cl-phenyl	2-(N-azetidinyl-methyl)phenyl
181	2-Cl-phenyl	2-(N-piperazinyl-methyl)phenyl
182	2-Cl-phenyl	2-(N,N'-BOC-piperazinyl-methyl)phenyl
183	2-Cl-phenyl	2-(N-imidazolyl-methyl)phenyl
184	2-Cl-phenyl	2-(N-methoxy-N-methylamino-methyl)phenyl
185	2-Cl-phenyl	2-(N-pyridonyl-methyl)phenyl
186	2-Cl-phenyl	2-(N-(N',N'-dimethylhydrazinyl-methyl)phenyl
187	2-Cl-phenyl	2-(amidinyl)phenyl
188	2-Cl-phenyl	2-(N-guanidinyl)phenyl
189	2-Cl-phenyl	2-(imidazolyl)phenyl
190	2-Cl-phenyl	2-(imidazolidinyl)phenyl
191	2-Cl-phenyl	2-(2-imidazolidinyl-sulfonyl)phenyl
192	2-Cl-phenyl	2-(2-pyrrolidinyl)phenyl
193	2-Cl-phenyl	2-(2-piperidinyl)phenyl
194	2-Cl-phenyl	2-(amidinyl-methyl)phenyl
195	2-Cl-phenyl	2-(2-imidazolidinyl-methyl)phenyl
196	2-Cl-phenyl	2-(N-(2-aminoimidazolyl)-methyl)phenyl
197	2-Cl-phenyl	2-dimethylaminoimidazol-1-yl
198	2-Cl-phenyl	2-(3-aminophenyl)
199	2-Cl-phenyl	2-(3-pyrrolidinylcarbonyl)
200	2-Cl-phenyl	2-glycinoyl
201	2-Cl-phenyl	2-(imidazol-1-ylacetyl)
202	2-F-phenyl	2-(N-pyrrolidinyl-methyl)phenyl
203	2-F-phenyl	2-(N-piperidinyl-methyl)phenyl
204	2-F-phenyl	2-(N-morpholino-methyl)phenyl
205	2-F-phenyl	2-(N,N'-methylmorpholinium-methyl)phenyl
206	2-F-phenyl	2-(N-pyridinium-methyl)phenyl
207	2-F-phenyl	2-(N-4-(N,N'-dimethylamino)-pyridinium-methyl)phenyl
208	2-F-phenyl	2-(N-azatanyl-methyl)phenyl
209	2-F-phenyl	2-(N-azetidinyl-methyl)phenyl
210	2-F-phenyl	2-(N-piperazinyl-methyl)phenyl
211	2-F-phenyl	2-(N,N'-BOC-piperazinyl-methyl)phenyl
212	2-F-phenyl	2-(N-imidazolyl-methyl)phenyl

213	2-F-phenyl	2-(N-methoxy-N-methylamino-methyl)phenyl
214	2-F-phenyl	2-(N-pyridonyl-methyl)phenyl
215	2-F-phenyl	2-(N-(N',N'-dimethylhydrazinyl-methyl)phenyl
216	2-F-phenyl	2-(amidinyl)phenyl
217	2-F-phenyl	2-(N-guanidinyl)phenyl
218	2-F-phenyl	2-(imidazolyl)phenyl
219	2-F-phenyl	2-(imidazolidinyl)phenyl
220	2-F-phenyl	2-(2-imidazolidinyl-sulfonyl)phenyl
221	2-F-phenyl	2-(2-pyrrolidinyl)phenyl
222	2-F-phenyl	2-(2-piperidinyl)phenyl
223	2-F-phenyl	2-(amidinyl-methyl)phenyl
224	2-F-phenyl	2-(2-imidazolidinyl-methyl)phenyl
225	2-F-phenyl	2-(N-(2-aminoimidazolyl)-methyl)phenyl
226	2-F-phenyl	2-dimethylaminoimidazol-1-yl
227	2-F-phenyl	2-(3-aminophenyl)
228	2-F-phenyl	2-(3-pyrrolidinylcarbonyl)
229	2-F-phenyl	2-glycinoyl
230	2-F-phenyl	2-(imidazol-1-ylacetyl)
231	2,5-diF-phenyl	2-(N-pyrrolidinyl-methyl)phenyl
232	2,5-diF-phenyl	2-(N-piperidinyl-methyl)phenyl
233	2,5-diF-phenyl	2-(N-morpholino-methyl)phenyl
234	2,5-diF-phenyl	2-(N,N'-methylmorpholinium-methyl)phenyl
235	2,5-diF-phenyl	2-(N-pyridinium-methyl)phenyl
236	2,5-diF-phenyl	2-(N-4-(N,N'-dimethylamino)-pyridinium-methyl)phenyl
237	2,5-diF-phenyl	2-(N-azatanyl-methyl)phenyl
238	2,5-diF-phenyl	2-(N-azetidinyl-methyl)phenyl
239	2,5-diF-phenyl	2-(N-piperazinyl-methyl)phenyl
240	2,5-diF-phenyl	2-(N,N'-BOC-piperazinyl-methyl)phenyl
241	2,5-diF-phenyl	2-(N-imidazolyl-methyl)phenyl
242	2,5-diF-phenyl	2-(N-methoxy-N-methylamino-methyl)phenyl
243	2,5-diF-phenyl	2-(N-pyridonyl-methyl)phenyl
244	2,5-diF-phenyl	2-(N-(N',N'-dimethylhydrazinyl-methyl)phenyl
245	2,5-diF-phenyl	2-(amidinyl)phenyl
246	2,5-diF-phenyl	2-(N-guanidinyl)phenyl
247	2,5-diF-phenyl	2-(imidazolyl)phenyl
248	2,5-diF-phenyl	2-(imidazolidinyl)phenyl
249	2,5-diF-phenyl	2-(2-imidazolidinyl-sulfonyl)phenyl
250	2,5-diF-phenyl	2-(2-pyrrolidinyl)phenyl
251	2,5-diF-phenyl	2-(2-piperidinyl)phenyl
252	2,5-diF-phenyl	2-(amidinyl-methyl)phenyl
253	2,5-diF-phenyl	2-(2-imidazolidinyl-methyl)phenyl
254	2,5-diF-phenyl	2-(N-(2-aminoimidazolyl)-methyl)phenyl
255	2,5-diF-phenyl	2-dimethylaminoimidazol-1-yl
256	2,5-diF-phenyl	2-(3-aminophenyl)
257	2,5-diF-phenyl	2-(3-pyrrolidinylcarbonyl)
258	2,5-diF-phenyl	2-glycinoyl
259	2,5-diF-phenyl	2-(imidazol-1-ylacetyl)

Table 3





Ex #	A	B
1	phenyl	2-(aminosulfonyl)phenyl
2	phenyl	2-(methylaminosulfonyl)phenyl
3	phenyl	1-pyrrolidinocarbonyl
4	phenyl	2-(methylsulfonyl)phenyl
5	phenyl	4-morpholino
6	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
7	phenyl	4-morpholinocarbonyl
8	2-pyridyl	2-(aminosulfonyl)phenyl
9	2-pyridyl	2-(methylaminosulfonyl)phenyl
10	2-pyridyl	1-pyrrolidinocarbonyl
11	2-pyridyl	2-(methylsulfonyl)phenyl
12	2-pyridyl	4-morpholino
13	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
14	2-pyridyl	4-morpholinocarbonyl
15	3-pyridyl	2-(aminosulfonyl)phenyl
16	3-pyridyl	2-(methylaminosulfonyl)phenyl
17	3-pyridyl	1-pyrrolidinocarbonyl
18	3-pyridyl	2-(methylsulfonyl)phenyl

19	3-pyridyl	4-morpholino
20	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
21	3-pyridyl	4-morpholinocarbonyl
22	2-pyrimidyl	2-(aminosulfonyl)phenyl
23	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
24	2-pyrimidyl	1-pyrrolidinocarbonyl
25	2-pyrimidyl	2-(methylsulfonyl)phenyl
26	2-pyrimidyl	4-morpholino
27	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
28	2-pyrimidyl	4-morpholinocarbonyl
29	5-pyrimidyl	2-(aminosulfonyl)phenyl
30	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
31	5-pyrimidyl	1-pyrrolidinocarbonyl
32	5-pyrimidyl	2-(methylsulfonyl)phenyl
33	5-pyrimidyl	4-morpholino
34	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
35	5-pyrimidyl	4-morpholinocarbonyl
36	2-Cl-phenyl	2-(aminosulfonyl)phenyl
37	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
38	2-Cl-phenyl	1-pyrrolidinocarbonyl
39	2-Cl-phenyl	2-(methylsulfonyl)phenyl
40	2-Cl-phenyl	4-morpholino
41	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
42	2-Cl-phenyl	4-morpholinocarbonyl
43	2-F-phenyl	2-(aminosulfonyl)phenyl
44	2-F-phenyl	2-(methylaminosulfonyl)phenyl
45	2-F-phenyl	1-pyrrolidinocarbonyl
46	2-F-phenyl	2-(methylsulfonyl)phenyl
47	2-F-phenyl	4-morpholino
48	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
49	2-F-phenyl	4-morpholinocarbonyl
50	2,5-diF-phenyl	2-(aminosulfonyl)phenyl
51	2,5-diF-phenyl	2-(methylaminosulfonyl)phenyl
52	2,5-diF-phenyl	1-pyrrolidinocarbonyl
53	2,5-diF-phenyl	2-(methylsulfonyl)phenyl
54	2,5-diF-phenyl	4-morpholino
55	2,5-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
56	2,5-diF-phenyl	4-morpholinocarbonyl
57	phenyl	2-(N-pyrrolidinyl-methyl)phenyl
58	phenyl	2-(N-piperidinyl-methyl)phenyl
59	phenyl	2-(N-morpholino-methyl)phenyl
60	phenyl	2-(N,N'-methylmorpholinium-methyl)phenyl
61	phenyl	2-(N-pyridinium-methyl)phenyl
62	phenyl	2-(N-4-(N,N'-dimethylamino)-pyridinium-methyl)phenyl
63	phenyl	2-(N-azatanyl-methyl)phenyl
64	phenyl	2-(N-azetidinyl-methyl)phenyl
65	phenyl	2-(N-piperazinyl-methyl)phenyl
66	phenyl	2-(N,N'-BOC-piperazinyl-methyl)phenyl
67	phenyl	2-(N-imidazolyl-methyl)phenyl
68	phenyl	2-(N-methoxy-N-methylamino-methyl)phenyl
69	phenyl	2-(N-pyridonyl-methyl)phenyl
70	phenyl	2-(N-(N',N'-dimethylhydrazinyl-methyl)phenyl
71	phenyl	2-(amidinyl)phenyl
72	phenyl	2-(N-guanidinyl)phenyl

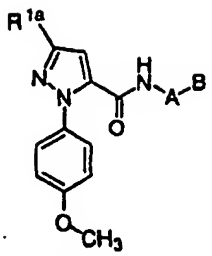
73	phenyl	2-(imidazolyl)phenyl
74	phenyl	2-(imidazolidinyl)phenyl
75	phenyl	2-(2-imidazolidinyl-sulfonyl)phenyl
76	phenyl	2-(2-pyrrolidinyl)phenyl
77	phenyl	2-(2-piperidinyl)phenyl
78	phenyl	2-(amidinyl-methyl)phenyl
79	phenyl	2-(2-imidazolidinyl-methyl)phenyl
80	phenyl	2-(N-(2-aminoimidazolyl)-methyl)phenyl
81	phenyl	2-dimethylaminoimidazol-1-yl
82	phenyl	2-(3-aminophenyl)
83	phenyl	2-(3-pyrrolidinylcarbonyl)
84	phenyl	2-glycinoyl
85	phenyl	2-(imidazol-1-ylacetyl)
86	2-pyridyl	2-(N-pyrrolidinyl-methyl)phenyl
87	2-pyridyl	2-(N-piperidinyl-methyl)phenyl
88	2-pyridyl	2-(N-morpholino-methyl)phenyl
89	2-pyridyl	2-(N,N'-methylmorpholinium-methyl)phenyl
90	2-pyridyl	2-(N-pyridinium-methyl)phenyl
91	2-pyridyl	2-(N-4-(N,N'-dimethylamino)-pyridinium-methyl)phenyl
92	2-pyridyl	2-(N-azatanyl-methyl)phenyl
93	2-pyridyl	2-(N-azetidinyl-methyl)phenyl
94	2-pyridyl	2-(N-piperazinyl-methyl)phenyl
95	2-pyridyl	2-(N,N'-BOC-piperazinyl-methyl)phenyl
96	2-pyridyl	2-(N-imidazolyl-methyl)phenyl
97	2-pyridyl	2-(N-methoxy-N-methylamino-methyl)phenyl
98	2-pyridyl	2-(N-pyridonyl-methyl)phenyl
99	2-pyridyl	2-(N-(N',N'-dimethylhydrazinyl-methyl)phenyl
100	2-pyridyl	2-(amidinyl)phenyl
101	2-pyridyl	2-(N-guanidinyl)phenyl
102	2-pyridyl	2-(imidazolyl)phenyl
103	2-pyridyl	2-(imidazolidinyl)phenyl
104	2-pyridyl	2-(2-imidazolidinyl-sulfonyl)phenyl
105	2-pyridyl	2-(2-pyrrolidinyl)phenyl
106	2-pyridyl	2-(2-piperidinyl)phenyl
107	2-pyridyl	2-(amidinyl-methyl)phenyl
108	2-pyridyl	2-(2-imidazolidinyl-methyl)phenyl
109	2-pyridyl	2-(N-(2-aminoimidazolyl)-methyl)phenyl
110	2-pyridyl	2-dimethylaminoimidazol-1-yl
111	2-pyridyl	2-(3-aminophenyl)
112	2-pyridyl	2-(3-pyrrolidinylcarbonyl)
113	2-pyridyl	2-glycinoyl
114	2-pyridyl	2-(imidazol-1-ylacetyl)
115	3-pyridyl	2-(N-pyrrolidinyl-methyl)phenyl
116	3-pyridyl	2-(N-piperidinyl-methyl)phenyl
117	3-pyridyl	2-(N-morpholino-methyl)phenyl
118	3-pyridyl	2-(N,N'-methylmorpholinium-methyl)phenyl
119	3-pyridyl	2-(N-pyridinium-methyl)phenyl
120	3-pyridyl	2-(N-4-(N,N'-dimethylamino)-pyridinium-methyl)phenyl
121	3-pyridyl	2-(N-azatanyl-methyl)phenyl
122	3-pyridyl	2-(N-azetidinyl-methyl)phenyl
123	3-pyridyl	2-(N-piperazinyl-methyl)phenyl
124	3-pyridyl	2-(N,N'-BOC-piperazinyl-methyl)phenyl
125	3-pyridyl	2-(N-imidazolyl-methyl)phenyl

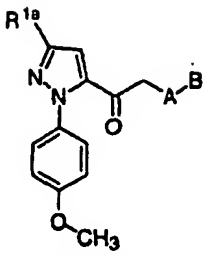
126	3-pyridyl	2-(N-methoxy-N-methylamino-methyl)phenyl
127	3-pyridyl	2-(N-pyridonyl-methyl)phenyl
128	3-pyridyl	2-(N-(N',N'-dimethylhydrazinyl-methyl)phenyl
129	3-pyridyl	2-(amidinyl)phenyl
130	3-pyridyl	2-(N-guanidinyl)phenyl
131	3-pyridyl	2-(imidazolyl)phenyl
132	3-pyridyl	2-(imidazolidinyl)phenyl
133	3-pyridyl	2-(2-imidazolidinyl-sulfonyl)phenyl
134	3-pyridyl	2-(2-pyrrolidinyl)phenyl
135	3-pyridyl	2-(2-piperidinyl)phenyl
136	3-pyridyl	2-(amidinyl-methyl)phenyl
137	3-pyridyl	2-(2-imidazolidinyl-methyl)phenyl
138	3-pyridyl	2-(N-(2-aminoimidazolyl)-methyl)phenyl
139	3-pyridyl	2-dimethylaminoimidazol-1-yl
140	3-pyridyl	2-(3-aminophenyl)
141	3-pyridyl	2-(3-pyrrolidinylcarbonyl)
142	3-pyridyl	2-glycinoyl
143	3-pyridyl	2-(imidazol-1-ylacetyl)
144	2-pyrimidyl	2-(N-pyrrolidinyl-methyl)phenyl
145	2-pyrimidyl	2-(N-piperidinyl-methyl)phenyl
146	2-pyrimidyl	2-(N-morpholino-methyl)phenyl
147	2-pyrimidyl	2-(N,N'-methylmorpholinium-methyl)phenyl
148	2-pyrimidyl	2-(N-pyridinium-methyl)phenyl
149	2-pyrimidyl	2-(N-4-(N,N'-dimethylamino)-pyridinium-methyl)phenyl
150	2-pyrimidyl	2-(N-azatanyl-methyl)phenyl
151	2-pyrimidyl	2-(N-azetidinyl-methyl)phenyl
152	2-pyrimidyl	2-(N-piperazinyl-methyl)phenyl
153	2-pyrimidyl	2-(N,N'-BOC-piperazinyl-methyl)phenyl
154	2-pyrimidyl	2-(N-imidazolyl-methyl)phenyl
155	2-pyrimidyl	2-(N-methoxy-N-methylamino-methyl)phenyl
156	2-pyrimidyl	2-(N-pyridonyl-methyl)phenyl
157	2-pyrimidyl	2-(N-(N',N'-dimethylhydrazinyl-methyl)phenyl
158	2-pyrimidyl	2-(amidinyl)phenyl
159	2-pyrimidyl	2-(N-guanidinyl)phenyl
160	2-pyrimidyl	2-(imidazolyl)phenyl
161	2-pyrimidyl	2-(imidazolidinyl)phenyl
162	2-pyrimidyl	2-(2-imidazolidinyl-sulfonyl)phenyl
163	2-pyrimidyl	2-(2-pyrrolidinyl)phenyl
164	2-pyrimidyl	2-(2-piperidinyl)phenyl
165	2-pyrimidyl	2-(amidinyl-methyl)phenyl
166	2-pyrimidyl	2-(2-imidazolidinyl-methyl)phenyl
167	2-pyrimidyl	2-(N-(2-aminoimidazolyl)-methyl)phenyl
168	2-pyrimidyl	2-dimethylaminoimidazol-1-yl
169	2-pyrimidyl	2-(3-aminophenyl)
170	2-pyrimidyl	2-(3-pyrrolidinylcarbonyl)
171	2-pyrimidyl	2-glycinoyl
172	2-pyrimidyl	2-(imidazol-1-ylacetyl)
173	2-Cl-phenyl	2-(N-pyrrolidinyl-methyl)phenyl
174	2-Cl-phenyl	2-(N-piperidinyl-methyl)phenyl
175	2-Cl-phenyl	2-(N-morpholino-methyl)phenyl
176	2-Cl-phenyl	2-(N,N'-methylmorpholinium-methyl)phenyl
177	2-Cl-phenyl	2-(N-pyridinium-methyl)phenyl
178	2-Cl-phenyl	2-(N-4-(N,N'-dimethylamino)-pyridinium-

		methyl)phenyl
179	2-Cl-phenyl	2-(N-azatanyl-methyl)phenyl
180	2-Cl-phenyl	2-(N-azetidinyl-methyl)phenyl
181	2-Cl-phenyl	2-(N-piperazinyl-methyl)phenyl
182	2-Cl-phenyl	2-(N,N'-BOC-piperazinyl-methyl)phenyl
183	2-Cl-phenyl	2-(N-imidazolyl-methyl)phenyl
184	2-Cl-phenyl	2-(N-methoxy-N-methylamino-methyl)phenyl
185	2-Cl-phenyl	2-(N-pyridonyl-methyl)phenyl
186	2-Cl-phenyl	2-(N-(N',N'-dimethylhydrazinyl-methyl)phenyl
187	2-Cl-phenyl	2-(amidinyl)phenyl
188	2-Cl-phenyl	2-(N-guanidinyl)phenyl
189	2-Cl-phenyl	2-(imidazolyl)phenyl
190	2-Cl-phenyl	2-(imidazolidinyl)phenyl
191	2-Cl-phenyl	2-(2-imidazolidinyl-sulfonyl)phenyl
192	2-Cl-phenyl	2-(2-pyrrolidinyl)phenyl
193	2-Cl-phenyl	2-(2-piperidinyl)phenyl
194	2-Cl-phenyl	2-(amidinyl-methyl)phenyl
195	2-Cl-phenyl	2-(2-imidazolidinyl-methyl)phenyl
196	2-Cl-phenyl	2-(N-(2-aminoimidazolyl)-methyl)phenyl
197	2-Cl-phenyl	2-dimethylaminoimidazol-1-yl
198	2-Cl-phenyl	2-(3-aminophenyl)
199	2-Cl-phenyl	2-(3-pyrrolidinylcarbonyl)
200	2-Cl-phenyl	2-glycinoyl
201	2-Cl-phenyl	2-(imidazol-1-ylacetyl)
202	2-F-phenyl	2-(N-pyrrolidinyl-methyl)phenyl
203	2-F-phenyl	2-(N-piperidinyl-methyl)phenyl
204	2-F-phenyl	2-(N-morpholino-methyl)phenyl
205	2-F-phenyl	2-(N,N'-methylmorpholinium-methyl)phenyl
206	2-F-phenyl	2-(N-pyridinium-methyl)phenyl
207	2-F-phenyl	2-(N-4-(N,N'-dimethylamino)-pyridinium-methyl)phenyl
208	2-F-phenyl	2-(N-azatanyl-methyl)phenyl
209	2-F-phenyl	2-(N-azetidinyl-methyl)phenyl
210	2-F-phenyl	2-(N-piperazinyl-methyl)phenyl
211	2-F-phenyl	2-(N,N'-BOC-piperazinyl-methyl)phenyl
212	2-F-phenyl	2-(N-imidazolyl-methyl)phenyl
213	2-F-phenyl	2-(N-methoxy-N-methylamino-methyl)phenyl
214	2-F-phenyl	2-(N-pyridonyl-methyl)phenyl
215	2-F-phenyl	2-(N-(N',N'-dimethylhydrazinyl-methyl)phenyl
216	2-F-phenyl	2-(amidinyl)phenyl
217	2-F-phenyl	2-(N-guanidinyl)phenyl
218	2-F-phenyl	2-(imidazolyl)phenyl
219	2-F-phenyl	2-(imidazolidinyl)phenyl
220	2-F-phenyl	2-(2-imidazolidinyl-sulfonyl)phenyl
221	2-F-phenyl	2-(2-pyrrolidinyl)phenyl
222	2-F-phenyl	2-(2-piperidinyl)phenyl
223	2-F-phenyl	2-(amidinyl-methyl)phenyl
224	2-F-phenyl	2-(2-imidazolidinyl-methyl)phenyl
225	2-F-phenyl	2-(N-(2-aminoimidazolyl)-methyl)phenyl
226	2-F-phenyl	2-dimethylaminoimidazol-1-yl
227	2-F-phenyl	2-(3-aminophenyl)
228	2-F-phenyl	2-(3-pyrrolidinylcarbonyl)
229	2-F-phenyl	2-glycinoyl
230	2-F-phenyl	2-(imidazol-1-ylacetyl)

231	2,5-diF-phenyl	2-(N-pyrrolidinyl-methyl)phenyl
232	2,5-diF-phenyl	2-(N-piperidinyl-methyl)phenyl
233	2,5-diF-phenyl	2-(N-morpholino-methyl)phenyl
234	2,5-diF-phenyl	2-(N,N'-methylmorpholinium-methyl)phenyl
235	2,5-diF-phenyl	2-(N-pyridinium-methyl)phenyl
236	2,5-diF-phenyl	2-(N-4-(N,N'-dimethylamino)-pyridinium-methyl)phenyl
237	2,5-diF-phenyl	2-(N-azatanyl-methyl)phenyl
238	2,5-diF-phenyl	2-(N-azetidinyl-methyl)phenyl
239	2,5-diF-phenyl	2-(N-piperazinyl-methyl)phenyl
240	2,5-diF-phenyl	2-(N,N'-BOC-piperazinyl-methyl)phenyl
241	2,5-diF-phenyl	2-(N-imidazolyl-methyl)phenyl
242	2,5-diF-phenyl	2-(N-methoxy-N-methylamino-methyl)phenyl
243	2,5-diF-phenyl	2-(N-pyridonyl-methyl)phenyl
244	2,5-diF-phenyl	2-(N-(N',N'-dimethylhydrazinyl-methyl)phenyl
245	2,5-diF-phenyl	2-(amidinyl)phenyl
246	2,5-diF-phenyl	2-(N-guanidinyl)phenyl
247	2,5-diF-phenyl	2-(imidazolyl)phenyl
248	2,5-diF-phenyl	2-(imidazolidinyl)phenyl
249	2,5-diF-phenyl	2-(2-imidazolidinyl-sulfonyl)phenyl
250	2,5-diF-phenyl	2-(2-pyrrolidinyl)phenyl
251	2,5-diF-phenyl	2-(2-piperidinyl)phenyl
252	2,5-diF-phenyl	2-(amidinyl-methyl)phenyl
253	2,5-diF-phenyl	2-(2-imidazolidinyl-methyl)phenyl
254	2,5-diF-phenyl	2-(N-(2-aminoimidazolyl)-methyl)phenyl
255	2,5-diF-phenyl	2-dimethylaminoimidazol-1-yl
256	2,5-diF-phenyl	2-(3-aminophenyl)
257	2,5-diF-phenyl	2-(3-pyrrolidinylcarbonyl)
258	2,5-diF-phenyl	2-glycinoyl
259	2,5-diF-phenyl	2-(imidazol-1-ylacetyl)

Table 4



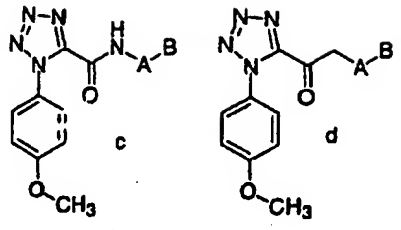


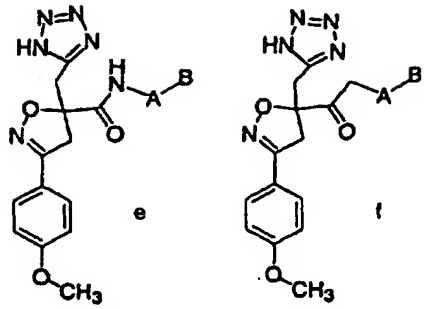
a_1 R^{1a}=CH_3	b_1 R^{1a}=CH_3
a_2 R^{1a}=CF_3	b_2 R^{1a}=CF_3
a_3 R^{1a}=SCH_3	b_3 R^{1a}=SCH_3
a_4 R^{1a}=$SOCH_3$	b_4 R^{1a}=$SOCH_3$
a_5 R^{1a}=SO_2CH_3	b_5 R^{1a}=SO_2CH_3
a_6 R^{1a}=Cl	b_6 R^{1a}=Cl
a_7 R^{1a}=Br	b_7 R^{1a}=Br
a_8 R^{1a}=CO_2CH_3	b_8 R^{1a}=CO_2CH_3
a_9 R^{1a}=CH_2OCH_3	b_9 R^{1a}=CH_2OCH_3

Ex#	A	B
1	phenyl	2-($(Me)_2N$-methyl)phenyl
2	phenyl	2-((Me)NH-methyl)phenyl
3	phenyl	2-(H_2N-methyl)phenyl
4	phenyl	2-$HOCH_2$-phenyl
5	2-F-phenyl	2-($(Me)_2N$-methyl)phenyl
6	2-F-phenyl	2-((Me)NH-methyl)phenyl
7	2-F-phenyl	2-(H_2N-methyl)phenyl
8	2-F-phenyl	2-$HOCH_2$-phenyl

9	phenyl	2-methylimidazol-1-yl
10	phenyl	2-ethylimidazol-1-yl
11	phenyl	2-((Me)$_2$N-methyl)imidazol-1-yl
12	phenyl	2-CH_3SO_2-imidazol-1-yl
13	phenyl	2-CH_3OCH_2-imidazol-1-yl
14	2-F-phenyl	2-methylimidazol-1-yl
15	2-F-phenyl	2-ethylimidazol-1-yl
16	2-F-phenyl	2-((Me)$_2$N-methyl)imidazol-1-yl
17	2-F-phenyl	2-CH_3SO_2-imidazol-1-yl
18	2-F-phenyl	2-CH_3OCH_2-imidazol-1-yl
19	2-Cl-phenyl	2-methylimidazol-1-yl
20	2-Cl-phenyl	2-ethylimidazol-1-yl
21	2-Cl-phenyl	2-((Me)$_2$N-methyl)imidazol-1-yl
22	2-Cl-phenyl	2-CH_3SO_2-imidazol-1-yl
23	2-Cl-phenyl	2-CH_3OCH_2-imidazol-1-yl
24	2-(Me)$_2$N-phenyl	2-methylimidazol-1-yl
25	2-(Me)$_2$N-phenyl	2-ethylimidazol-1-yl
26	2-(Me)$_2$N-phenyl	2-((Me)$_2$N-methyl)imidazol-1-yl
27	2-(Me)$_2$N-phenyl	2-CH_3SO_2-imidazol-1-yl
28	2-(Me)$_2$N-phenyl	2-CH_3OCH_2-imidazol-1-yl
29	phenyl	N-methylimidazol-2-yl
30	phenyl	4-methylimidazol-5-yl
31	phenyl	5-CF_3-pyrazol-1-yl
32	2-F-phenyl	N-methylimidazol-2-yl
33	2-F-phenyl	4-methylimidazol-5-yl
34	2-F-phenyl	5-CF_3-pyrazol-1-yl
35	phenyl	guanidino
36	phenyl	2-thiazolin-2-ylamine
37	phenyl	N-methyl-2-imidazolin-2-yl
38	phenyl	N-methyl-1,4,5,6-tetrahydropyrimid-2-yl
39	phenyl	N-methylimidazol-2-ylthiol
40	phenyl	t-butoxycarbonylamine
41	phenyl	(N-pyrrolidino)formylimino
42	phenyl	(N-pyrrolidino)formyl-N-methanesulfamoyl)imino
43	2-F-phenyl	guanidino
44	2-F-phenyl	2-thiazolin-2-ylamine
45	2-F-phenyl	N-methyl-2-imidazolin-2-yl
46	2-F-phenyl	N-methyl-1,4,5,6-tetrahydropyrimid-2-yl
47	2-F-phenyl	N-methylimidazol-2-ylthio
48	2-F-phenyl	t-butoxycarbonylamine
49	2-F-phenyl	(N-pyrrolidino)formylimino
50	2-F-phenyl	(N-pyrrolidino)formyl-N-methanesulfamoyl)imino
51	2-CH_3O-phenyl	(N-pyrrolidino)formylimino
52	2-CH_3O-phenyl	(N-pyrrolidino)formyl-N-(methanesulfamoyl)imino

Table 5

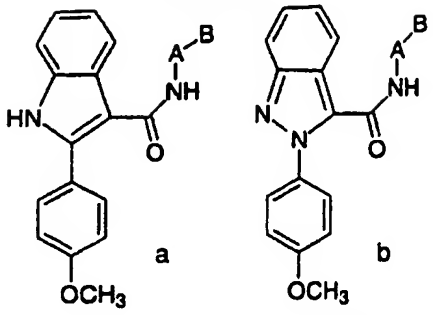


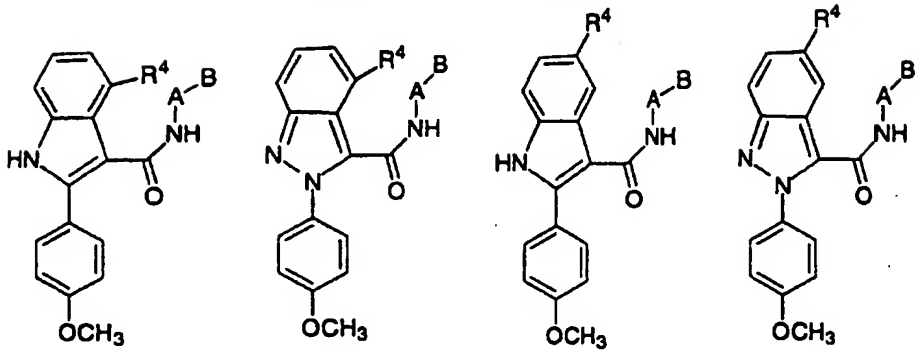


Ex#	A	B
1	phenyl	2-((Me)$_2$N-methyl)phenyl
2	phenyl	2-((Me)NH-methyl)phenyl
3	phenyl	2-(H_2N-methyl)phenyl
4	phenyl	2-$HOCH_2$-phenyl
5	2-F-phenyl	2-((Me)$_2$N-methyl)phenyl
6	2-F-phenyl	2-((Me)NH-methyl)phenyl
7	2-F-phenyl	2-(H_2N-methyl)phenyl
8	2-F-phenyl	2-$HOCH_2$-phenyl
9	phenyl	2-methylimidazol-1-yl
10	phenyl	2-ethylimidazol-1-yl
11	phenyl	2-((Me)$_2$N-methyl)imidazol-1-yl
12	phenyl	2-CH_3SO_2-imidazol-1-yl
13	phenyl	2-CH_3OCH_2-imidazol-1-yl
14	2-F-phenyl	2-methylimidazol-1-yl
15	2-F-phenyl	2-ethylimidazol-1-yl
16	2-F-phenyl	2-((Me)$_2$N-methyl)imidazol-1-yl
17	2-F-phenyl	2-CH_3SO_2-imidazol-1-yl

18	2-F-phenyl	2-CH_3OCH_2-imidazol-1-yl
19	2-Cl-phenyl	2-methylimidazol-1-yl
20	2-Cl-phenyl	2-ethylimidazol-1-yl
21	2-Cl-phenyl	2-((Me)$_2$N-methyl)imidazol-1-yl
22	2-Cl-phenyl	2-CH_3SO_2-imidazol-1-yl
23	2-Cl-phenyl	2-CH_3OCH_2-imidazol-1-yl
24	2-(Me)$_2$N-phenyl	2-methylimidazol-1-yl
25	2-(Me)$_2$N-phenyl	2-ethylimidazol-1-yl
26	2-(Me)$_2$N-phenyl	2-((Me)$_2$N-methyl)imidazol-1-yl
27	2-(Me)$_2$N-phenyl	2-CH_3SO_2-imidazol-1-yl
28	2-(Me)$_2$N-phenyl	2-CH_3OCH_2-imidazol-1-yl
29	phenyl	N-methylimidazol-2-yl
30	phenyl	4-methylimidazol-5-yl
31	phenyl	5-CF_3-pyrazol-1-yl
32	2-F-phenyl	N-methylimidazol-2-yl
33	2-F-phenyl	4-methylimidazol-5-yl
34	2-F-phenyl	5-CF_3-pyrazol-1-yl
35	phenyl	guanidino
36	phenyl	2-thiazolin-2-ylamine
37	phenyl	N-methyl-2-imidazolin-2-yl
38	phenyl	N-methyl-1,4,5,6-tetrahydropyrimid-2-yl
39	phenyl	N-methylimidazol-2-ylthiol
40	phenyl	t-butoxycarbonylamine
41	phenyl	(N-pyrrolidino)formylimino
42	phenyl	(N-pyrrolidino)formyl-N-methanesulfamoyl)imino
43	2-F-phenyl	guanidino
44	2-F-phenyl	2-thiazolin-2-ylamine
45	2-F-phenyl	N-methyl-2-imidazolin-2-yl
46	2-F-phenyl	N-methyl-1,4,5,6-tetrahydropyrimid-2-yl
47	2-F-phenyl	N-methylimidazol-2-ylthio
48	2-F-phenyl	t-butoxycarbonylamine
49	2-F-phenyl	(N-pyrrolidino)formylimino
50	2-F-phenyl	(N-pyrrolidino)formyl-N-methanesulfamoyl)imino
51	2-CH_3O-phenyl	(N-pyrrolidino)formylimino
52	2-CH_3O-phenyl	(N-pyrrolidino)formyl-N-(methanesulfamoyl)imino

Table 6





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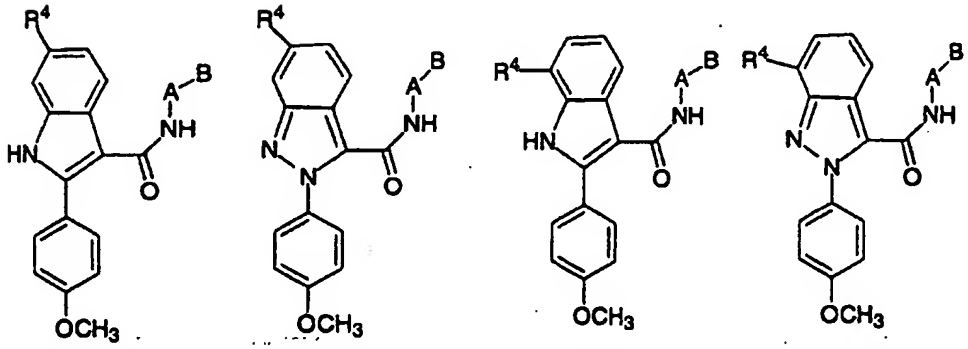
c_2 R^4=CO_2CH_3
c_3 R^4= CH_2OCH_3
c_4 R^4=CH_3
c_5 R^4=CF_3
c_6 R^4=Cl
c_7 R^4=F

d_1 R^4=OCH_3
d_2 R^4=CO_2CH_3
d_3 R^4= CH_2OCH_3
d_4 R^4=CH_3
d_5 R^4=CF_3
d_6 R^4=Cl
d_7 R^4=F

e_1 R^4=OCH_3
e_2 R^4=CO_2CH_3
e_3 R^4= CH_2OCH_3
e_4 R^4=CH_3
e_5 R^4=CF_3
e_6 R^4=Cl
e_7 R^4=F

f_1 R^4=OCH_3
f_2 R^4=CO_2CH_3
f_3 R^4= CH_2OCH_3
f_4 R^4=CH_3
f_5 R^4=CF_3
f_6 R^4=Cl
f_7 R^4=F



g_1 R^4=OCH_3
g_2 R^4=CO_2CH_3
g_3 R^4= CH_2OCH_3
g_4 R^4=CH_3
g_5 R^4=CF_3
g_6 R^4=Cl
g_7 R^4=F

h_1 R^4=OCH_3
h_2 R^4=CO_2CH_3
h_3 R^4= CH_2OCH_3
h_4 R^4=CH_3
h_5 R^4=CF_3
h_6 R^4=Cl
h_7 R^4=F

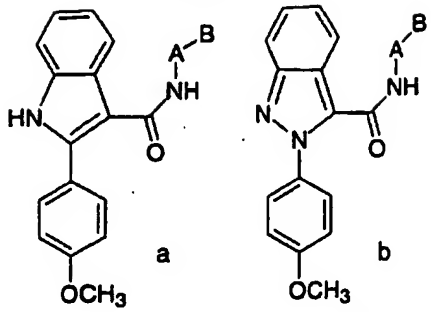
i_1 R^4=OCH_3
i_2 R^4=CO_2CH_3
i_3 R^4= CH_2OCH_3
i_4 R^4=CH_3
i_5 R^4=CF_3
i_6 R^4=Cl
i_7 R^4=F

j_1 R^4=OCH_3
j_2 R^4=CO_2CH_3
j_3 R^4= CH_2OCH_3
j_4 R^4=CH_3
j_5 R^4=CF_3
j_6 R^4=Cl
j_7 R^4=F

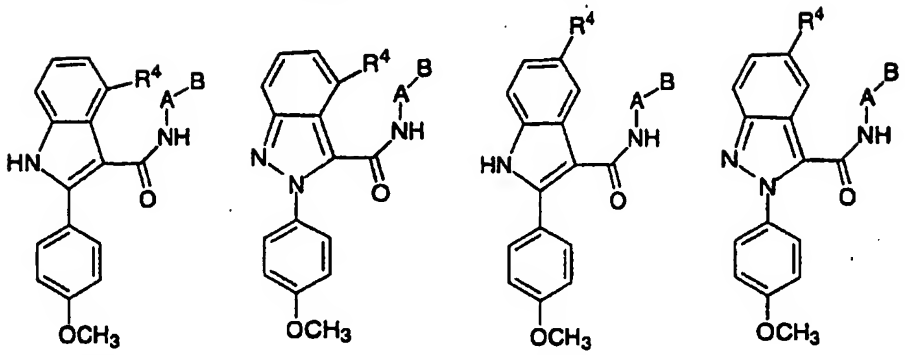
Ex #	A	B
1	phenyl	2-(aminosulfonyl)phenyl
2	phenyl	2-(methylaminosulfonyl)phenyl
3	phenyl	1-pyrrolidinocarbonyl
4	phenyl	2-(methylsulfonyl)phenyl
5	phenyl	4-morpholino
6	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
7	phenyl	4-morpholinocarbonyl
8	2-pyridyl	2-(aminosulfonyl)phenyl
9	2-pyridyl	2-(methylaminosulfonyl)phenyl
10	2-pyridyl	1-pyrrolidinocarbonyl
11	2-pyridyl	2-(methylsulfonyl)phenyl
12	2-pyridyl	4-morpholino
13	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
14	2-pyridyl	4-morpholinocarbonyl
15	3-pyridyl	2-(aminosulfonyl)phenyl
16	3-pyridyl	2-(methylaminosulfonyl)phenyl
17	3-pyridyl	1-pyrrolidinocarbonyl
18	3-pyridyl	2-(methylsulfonyl)phenyl
19	3-pyridyl	4-morpholino
20	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
21	3-pyridyl	4-morpholinocarbonyl
22	2-pyrimidyl	2-(aminosulfonyl)phenyl
23	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
24	2-pyrimidyl	1-pyrrolidinocarbonyl
25	2-pyrimidyl	2-(methylsulfonyl)phenyl
26	2-pyrimidyl	4-morpholino
27	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
28	2-pyrimidyl	4-morpholinocarbonyl
29	5-pyrimidyl	2-(aminosulfonyl)phenyl
30	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
31	5-pyrimidyl	1-pyrrolidinocarbonyl
32	5-pyrimidyl	2-(methylsulfonyl)phenyl
33	5-pyrimidyl	4-morpholino
34	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
35	5-pyrimidyl	4-morpholinocarbonyl
36	2-Cl-phenyl	2-(aminosulfonyl)phenyl
37	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
38	2-Cl-phenyl	1-pyrrolidinocarbonyl
39	2-Cl-phenyl	2-(methylsulfonyl)phenyl
40	2-Cl-phenyl	4-morpholino
41	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
42	2-Cl-phenyl	4-morpholinocarbonyl
43	2-F-phenyl	2-(aminosulfonyl)phenyl
44	2-F-phenyl	2-(methylaminosulfonyl)phenyl
45	2-F-phenyl	1-pyrrolidinocarbonyl
46	2-F-phenyl	2-(methylsulfonyl)phenyl
47	2-F-phenyl	4-morpholino
48	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
49	2-F-phenyl	4-morpholinocarbonyl
50	2,5-diF-phenyl	2-(aminosulfonyl)phenyl
51	2,5-diF-phenyl	2-(methylaminosulfonyl)phenyl
52	2,5-diF-phenyl	1-pyrrolidinocarbonyl
53	2,5-diF-phenyl	2-(methylsulfonyl)phenyl

54	2,5-diF-phenyl	4-morpholino
55	2,5-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
56	2,5-diF-phenyl	4-morpholinocarbonyl

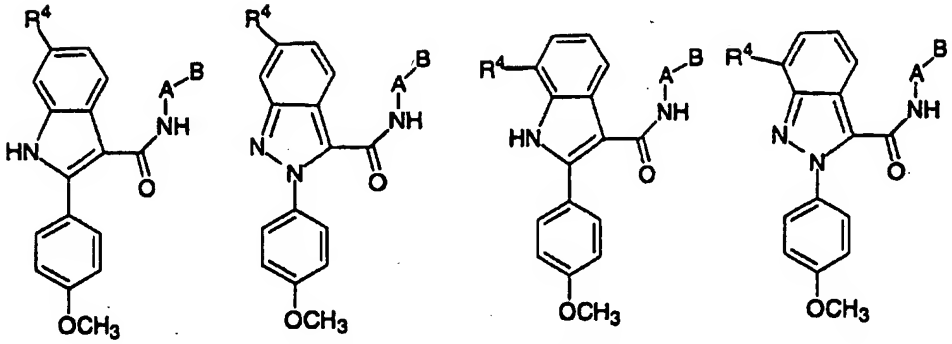
Table 7



a b



c_1 R^4=OCH_3	d_1 R^4=OCH_3	e_1 R^4=OCH_3	f_1 R^4=OCH_3
c_2 R^4=CO_2CH_3	d_2 R^4=CO_2CH_3	e_2 R^4=CO_2CH_3	f_2 R^4=CO_2CH_3
c_3 R^4= CH_2OCH_3	d_3 R^4= CH_2OCH_3	e_3 R^4= CH_2OCH_3	f_3 R^4= CH_2OCH_3
c_4 R^4=CH_3	d_4 R^4=CH_3	e_4 R^4=CH_3	f_4 R^4=CH_3
c_5 R^4=CF_3	d_5 R^4=CF_3	e_5 R^4=CF_3	f_5 R^4=CF_3
c_6 R^4=Cl	d_6 R^4=Cl	e_6 R^4=Cl	f_6 R^4=Cl
c_7 R^4=F	d_7 R^4=F	e_7 R^4=F	f_7 R^4=F



g_1 R^4=OCH_3	h_1 R^4=OCH_3	i_1 R^4=OCH_3	j_1 R^4=OCH_3
g_2 R^4=CO_2CH_3	h_2 R^4=CO_2CH_3	i_2 R^4=CO_2CH_3	j_2 R^4=CO_2CH_3
g_3 R^4= CH_2OCH_3	h_3 R^4= CH_2OCH_3	i_3 R^4= CH_2OCH_3	j_3 R^4= CH_2OCH_3
g_4 R^4=CH_3	h_4 R^4=CH_3	i_4 R^4=CH_3	j_4 R^4=CH_3
g_5 R^4=CF_3	h_5 R^4=CF_3	i_5 R^4=CF_3	j_5 R^4=CF_3
g_6 R^4=Cl	h_6 R^4=Cl	i_6 R^4=Cl	j_6 R^4=Cl
g_7 R^4=F	h_7 R^4=F	i_7 R^4=F	j_7 R^4=F

Ex#	A	B
1	phenyl	2-((Me)$_2$N-methyl)phenyl
2	phenyl	2-((Me)NH-methyl)phenyl
3	phenyl	2-(H_2N-methyl)phenyl
4	phenyl	2-$HOCH_2$-phenyl
5	2-F-phenyl	2-((Me)$_2$N-methyl)phenyl
6	2-F-phenyl	2-((Me)NH-methyl)phenyl
7	2-F-phenyl	2-(H_2N-methyl)phenyl
8	2-F-phenyl	2-$HOCH_2$-phenyl
9	phenyl	2-methylimidazol-1-yl
10	phenyl	2-ethylimidazol-1-yl
11	phenyl	2-((Me)$_2$N-methyl)imidazol-1-yl
12	phenyl	2-CH_3SO_2-imidazol-1-yl
13	phenyl	2-CH_3OCH_2-imidazol-1-yl
14	2-F-phenyl	2-methylimidazol-1-yl
15	2-F-phenyl	2-ethylimidazol-1-yl
16	2-F-phenyl	2-((Me)$_2$N-methyl)imidazol-1-yl
17	2-F-phenyl	2-CH_3SO_2-imidazol-1-yl
18	2-F-phenyl	2-CH_3OCH_2-imidazol-1-yl
19	2-Cl-phenyl	2-methylimidazol-1-yl
20	2-Cl-phenyl	2-ethylimidazol-1-yl
21	2-Cl-phenyl	2-((Me)$_2$N-methyl)imidazol-1-yl
22	2-Cl-phenyl	2-CH_3SO_2-imidazol-1-yl
23	2-Cl-phenyl	2-CH_3OCH_2-imidazol-1-yl
24	2-(Me)$_2$N-phenyl	2-methylimidazol-1-yl
25	2-(Me)$_2$N-phenyl	2-ethylimidazol-1-yl
26	2-(Me)$_2$N-phenyl	2-((Me)$_2$N-methyl)imidazol-1-yl
27	2-(Me)$_2$N-phenyl	2-CH_3SO_2-imidazol-1-yl
28	2-(Me)$_2$N-phenyl	2-CH_3OCH_2-imidazol-1-yl
29	phenyl	N-methylimidazol-2-yl
30	phenyl	4-methylimidazol-5-yl
31	phenyl	5-CF_3-pyrazol-1-yl
32	2-F-phenyl	N-methylimidazol-2-yl
33	2-F-phenyl	4-methylimidazol-5-yl
34	2-F-phenyl	5-CF_3-pyrazol-1-yl
35	phenyl	guanidino
36	phenyl	2-thiazolin-2-ylamine
37	phenyl	N-methyl-2-imidazolin-2-yl
38	phenyl	N-methyl-1,4,5,6-tetrahydropyrimid-2-yl
39	phenyl	N-methylimidazol-2-ylthiol
40	phenyl	t-butoxycarbonylamine
41	phenyl	(N-pyrrolidino)formylimino
42	phenyl	(N-pyrrolidino)formyl-N-methanesulfamoyl)imino
43	2-F-phenyl	guanidino
44	2-F-phenyl	2-thiazolin-2-ylamine
45	2-F-phenyl	N-methyl-2-imidazolin-2-yl
46	2-F-phenyl	N-methyl-1,4,5,6-tetrahydropyrimid-2-yl
47	2-F-phenyl	N-methylimidazol-2-ylthio
48	2-F-phenyl	t-butoxycarbonylamine
49	2-F-phenyl	(N-pyrrolidino)formylimino

50	2-F-phenyl	(N-pyrrolidino)formyl-N-methanesulfamoyl)imino
51	2-CH_3O-phenyl	(N-pyrrolidino)formylimino
52	2-CH_3O-phenyl	(N-pyrrolidino)formyl-N-(methanesulfamoyl)imino

Utility

[0322] The compounds of this invention are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals. The term "thromboembolic disorders" as used herein includes arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example, unstable angina, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, cerebral embolism, kidney embolisms, and pulmonary embolisms. The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of factor Xa or thrombin.

[0323] The effectiveness of compounds of the present invention as inhibitors of factor Xa was determined using purified human factor Xa and synthetic substrate. The rate of factor Xa hydrolysis of chromogenic substrate S2222 (Kabi Pharmacia, Franklin, OH) was measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA, which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nM. A decrease in the rate of absorbance change at 405 nm in the presence of inhibitor is indicative of enzyme inhibition. The results of this assay are expressed as inhibitory constant, Ki.

[0324] Factor Xa determinations were made in 0.10 M sodium phosphate buffer, pH 7.5, containing 0.20 M NaCl, and 0.5 % PEG 8000. The Michaelis constant, K_m, for substrate hydrolysis was determined at 25°C using the method of Lineweaver and Burk. Values of K_i were determined by allowing 0.2-0.5 nM human factor Xa (Enzyme Research Laboratories, South Bend, IN) to react with the substrate (0.20 mM-1 mM) in the presence of inhibitor. Reactions were allowed to go for 30 minutes and the velocities (rate of absorbance change vs time) were measured in the time frame of 25-30 minutes. The following relationship was used to calculate Ki values:

$$(v_o - v_s)/v_s = I/(K_i\,(1 + S/K_m))$$

where:

v_o is the velocity of the control in the absence of inhibitor;
v_s is the velocity in the presence of inhibitor;
I is the concentration of inhibitor;
K_i is the dissociation constant of the enzyme:inhibitor complex;
S is the concentration of substrate;
K_m is the Michaelis constant.

Using the methodology described above, a number of compounds of the present invention were found to exhibit a K_i of ≤15 μM, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.

[0325] The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arteriovenous (AV) shunt thrombosis model. In this model, rabbits weighing 2-3 kg anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (50 mg/kg i.m.) are used. A saline-filled AV shunt device is connected between the femoral arterial and the femoral venous cannulae. The AV shunt device consists of a piece of 6-cm tygon tubing which contains a piece of silk thread. Blood will flow from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to a silk thread will induce the formation of a significant thrombus. After forty minutes, the shunt is disconnected and the silk thread covered with thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of thrombus formation is determined for each treatment group.

[0326] The ID50 values (dose which produces 50% inhibition of thrombus formation) are estimated by linear regression.

[0327] The compounds of formula (I) may also be useful as inhibitors of serine proteases, notably human thrombin, plasma kallikrein and plasmin. Because of their inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological reactions, blood coagulation and inflammation, catalyzed by the aforesaid class

of enzymes. Specifically, the compounds have utility as drugs for the treatment of diseases arising from elevated thrombin activity such as myocardial infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.

[0328] Some compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin by their ability to inhibit the cleavage of small molecule substrates by thrombin in a purified system. In vitro inhibition constants were determined by the method described by Kettner et al. in *J. Biol. Chem.* **265**, 18289-18297 (1990).

[0329] In these assays, thrombin-mediated hydrolysis of the chromogenic substrate S2238 (Helena Laboratories, Beaumont, TX) was monitored spectrophotometrically. Addition of an inhibitor to the assay mixture results in decreased absorbance and is indicative of thrombin inhibition. Human thrombin (Enzyme Research Laboratories, Inc., South Bend, IN) at a concentration of 0.2 nM in 0.10 M sodium phosphate buffer, pH 7.5, 0.20 M NaCl. and 0.5% PEG 6000, was incubated with various substrate concentrations ranging from 0.20 to 0.02 mM. After 25 to 30 minutes of incubation, thrombin activity was assayed by monitoring the rate of increase in absorbance at 405 nm which arises owing to substrate hydrolysis. Inhibition constants were derived from reciprocal plots of the reaction velocity as a function of substrate concentration using the standard method of Lineweaver and Burk. Using the methodology described above, some compounds of this invention were evaluated and found to exhibit a K_i of less than 15 μm, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.

[0330] The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. These include other anti-coagulant or coagulation inhibitory agents, anti-platelet or platelet inhibitory agents, thrombin inhibitors, or thrombolytic or fibrinolytic agents.

[0331] The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically effective amount" it is meant an amount of a compound of Formula I that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

[0332] By "administered in combination" or "combination therapy" it is meant that the compound of Formula I and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. Other anticoagulant agents (or coagulation inhibitory agents) that may be used in combination with the compounds of this invention include warfarin and heparin, as well as other factor Xa inhibitors such as those described in the publications identified above under Background of the Invention.

[0333] The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include, but are not limited to, the various known non-steroidal antiinflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA), and piroxicam are preferred. Other suitable anti-platelet agents include ticlopidine, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine is also a preferred compound since it is known to be gentle on the gastro-intestinal tract in use. Still other suitable platelet inhibitory agents include IIb/IIIa antagonists, thromboxane-A2-receptor antagonists and thromboxane-A2-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

[0334] The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are not limited to, boroarginine derivatives, boropeptides, heparins, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal a-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin. Boropeptide thrombin inhibitors include compounds described in Kettner et al., U.S. Patent No. 5,187,157 and European Patent Application Publication Number 293 881 A2.

[0335] Other suitable boroarginine derivatives and boropeptide thrombin inhibitors include those disclosed in PCT Application Publication Number 92/07869 and European Patent Application Publication Number 471,651 A2.

[0336] The term thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator, anistreplase, urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in European Patent Application

No. 028,489.

[0337] The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

[0338] Administration of the compounds of Formula I of the invention in combination with such additional therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety.

[0339] The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of factor Xa. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving factor Xa. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

[0340] The compounds of the present invention may also be used in diagnostic assays involving factor Xa. For example, the presence of factor Xa in an unknown sample could be determined by addition of chromogenic substrate S2222 to a series of solutions containing test sample and optionally one of the compounds of the present invention. If production of pNA is observed in the solutions containing test sample, but no compound of the present invention, then one would conclude factor Xa was present.

Dosage and Formulation

[0341] The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

[0342] The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient,and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

[0343] By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

[0344] Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

[0345] The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

[0346] For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cel-

lulose, agar, bentonite, xanthan gum, and the like.

[0347] The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

[0348] Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

[0349] Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

[0350] Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

[0351] Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

[0352] In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl-or propyl-paraben, and chlorobutanol.

[0353] Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

[0354] Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

[0355] A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

[0356] A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

[0357] Tablets may be prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

[0358] A parenteral composition suitable for administration by injection may be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution should be made isotonic with sodium chloride and sterilized.

Suspension

[0359] An aqueous suspension can be prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

[0360] Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of Formula I and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

[0361] Where the compounds of Formula I are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of Formula I and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

[0362] Where the compounds of Formula I are adminstered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of Formula I, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolyic agent when administered alone may be reduced by about 70-80% when administered with a compound of Formula I.

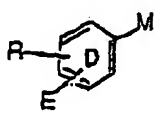
[0363] Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

[0364] Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

[0365] These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

Claims

1. A compound of formula I:



I

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

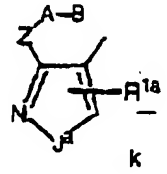
ring D is phenyl or pyridyl:

E is selected from F, Cl, Br, I, OH, C_{1-3} alkoxy, SH, C_{1-3} alkyl-S, $S(O)R^{2b}$, $S(O)_2R^{3a}$, $S(O)_2NR^2R^{2a}$, and OCF_3;

R is selected from H, F, Cl, Br, I, OR^3, SR^3, NO_2, and CH_2OR^3;

alternatively, E and R combine to form methylenedioxy or ethylenedioxy;

M is selected from the group: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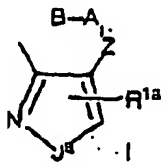
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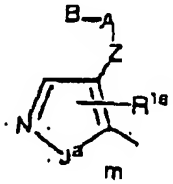
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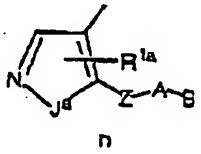
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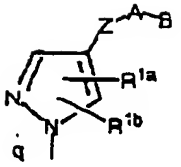
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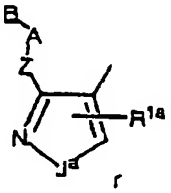
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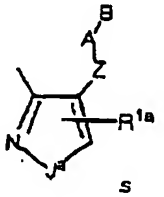
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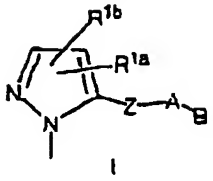
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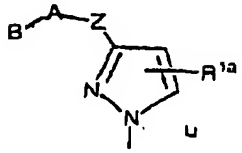
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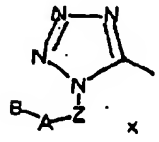
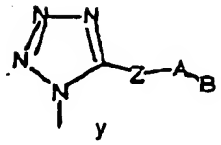

x

and


y

J^a is NH or NR^{1a};

Z is selected from C_{1-4} alkylene, $(CH_2)_rO(CH_2)_r$, $(CH_2)_rNR^3(CH_2)_r$, $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)O(CH_2)_r$, $(CH_2)_rOC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_rNR^3C(O)(CH_2)_r$, $(CH_2)_rOC(O)O(CH_2)_r$, $(CH_2)_rOC(O)NR^3(CH_2)_r$, $(CH_2)_rNR^3C(O)O(CH_2)_r$, $(CH_2)_rNR^3C(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, $(CH_2)_rSO_2NR^3(CH_2)_r$, $(CH_2)_rNR^3SO_2(CH_2)_r$, and $(CH_2)_rNR^3SO_2NR^3(CH_2)_r$, provided that Z does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with ring-M or group A;

R^{1a} and R^{1b} are indeperdently absent or selected from $-(CH_2)_r-R^{1'}$, $-CH=CH-R^{1'}$, $NCH_2R^{1''}$, $OCH_2R^{1''}$, $SCH_2R^{1''}$, $NH(CH_2)_2(CH_2)_tR^{1'}$, $C(CH_2)_2(CH_2)_tR^{1'}$, and $S(CH_2)_2(CH_2)_tR^{1'}$;

alternatively, R^{1a} and R^{1b}, when attached to adjacent carbon atoms, together with the atoms to which they are attached form a 5-8 membered saturated partially saturated or unsaturated ring substituted with 0-2 R^4 and which contains from 0-2 heteroatoms selected from the group consisting of N, O, and S;

alternatively, when Z is C(O)NH and R^{1a} is attached to a ring carbon adjacent to Z, then R^{1a} is a C(O) which replaces the amide hydrogen of Z to form a cyclic imide;

$R^{1'}$ is selected from H, C_{1-3} alkyl, F, Cl, Br, I, -CN, -CHO, $(CF_2)_rCF_3$, $(CH_2)_rCR^2$, NR^2R^{2a}, $C(O)R^{2c}$, $OC(O)R^2$, $(CF_2)_rCO_2R^{2c}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $CH(=NR^{2c})NR^2R^{2a}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^{2b}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^{2a}R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$, $NR^2SO_2R^{2b}$, C_{3-6} carbocyclic residue substituted with 0-2 R^4, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

$R^{1''}$ is selected from H, $CH(CH_2OR^2)_2$, $C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $S(O)R^{2b}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;

R^2, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2a}, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, phenethyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-5} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl,

R^{3b}, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3c}, at each occurrence, is selected from C_{1-4} alkyl, and phenyl;

A is selected from:

- C_{3-10} carbocyclic residue substituted with 0-2 R^4, and
- 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

B is selected from: Y and X-Y;

X is selected from C_{1-4} alkylene, $-CR^2(CR^2R^{2b})(CH_2)_t-$, -C(O)-, -C (=$NR^{1'}$)-, $-CR^2(NR^{1''}R^2)-$, $-CR^2(OR^2)-$, $-CR^2(SR^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-S(O)_p-$, $-S(O)_pCR^2R^{2a}-$, $-CR^2R^{2a}S(O)_p-$, $-S(O)_2NR^2-$, $-NR^2S(O)_2-$, $-NR^2S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S(O)_2NR^2-$, $-NR^2S(O)_2NR^2-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)O-$, $-OC(O)NR^2-$, $-NR^2C(O)NR^2-$, $-NR^2-$,

$-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

Y is selected from:

$(CH_2)_rNR^2R^{2a}$, provided that X-Y do not form a N-N, O-N, or S-N bond,
C_{3-10} carbocyclic residue substituted with 0-2 R^{4a}, and
5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, CH $(=NR^2)NR^2R^{2a}$, CH $(=NS(O)_2R^5)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $C(O)NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, $(CF_2)_rCF_3$, NCH_2R^{1*}, OCH_2R^{1*}, SCH_2R^{1*}, $N(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$, and S $(CH_2)_2(CH_2)_tR^{1'}$,

alternatively, one R^4 is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, $(CH_2)_r$-F, $(CH_2)_r$-Br, $(CH_2)_r$-Cl, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rNR^2R^{2b}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $C(O)NHSO_2$-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, and $(CF_2)_rCF_3$;

alternatively, one R^{4a} is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-1 R^5;

R^{4b}, at each occurrence, is selected from H, =O, $(CH_2)_rCR^3$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $CH(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, and $(CF_2)_rCF_3$;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

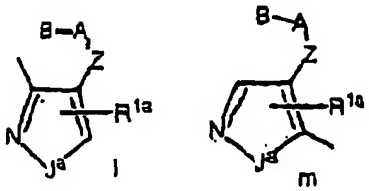
R^6, at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;

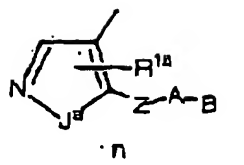
p is selected from 0, 1, and 2;

r is selected from 0, 1, 2, and 3;
and,

t is selected from 0 and 1.

2. A compound according to Claim 1, wherein M is selected from the group:





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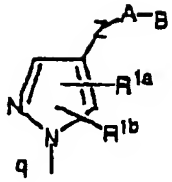

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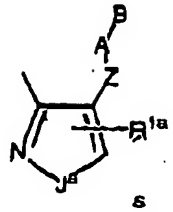

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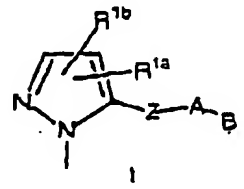

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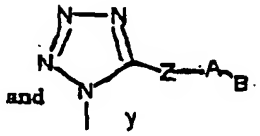
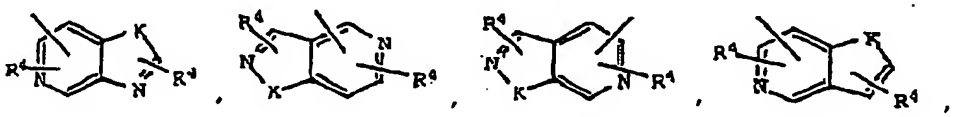


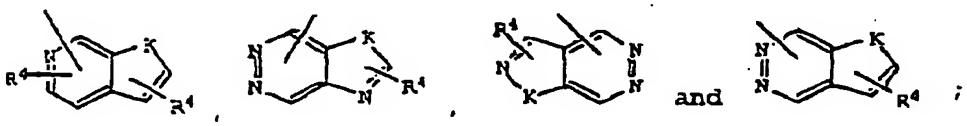
and y

Z is selected from $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)O(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, and $(CH_2)_rSO_2NR^3(CH_2)_r$; and,

Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0~2 R^{4a}; phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, benzofuran, benzothiofuran, indole, benzimidazole, benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole, and isoindazole;

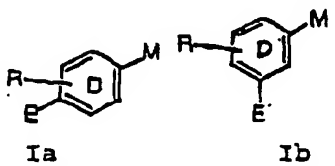
Y may also be selected from the following bicyclic heteroaryl ring systems:





K is selected from O, S, NH, and N.

3. A compound according to Claim 2, wherein the compound is of formula Ia or Ib:



Ia Ib

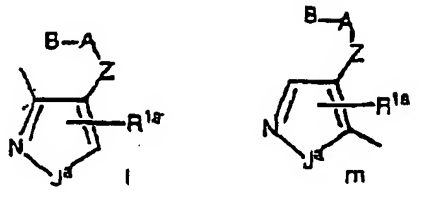
wherein;

ring D is phenyl or pyridyl:

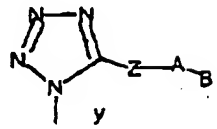
E is selected from F, Cl, Br, and C_{1-3} alkoxy;

R is selected from H, F, Cl, Br, OR^3, and CH_2OR^3;

M is selected from the group:



and



Z is selected from $(CH_2)_rC(O)(CH_2)_r$ and $(CH_2)_rC(O)NR^3(CH_2)_r$; and,

Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a}; phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-chiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-chiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-criazole, 1,3,4-triazole, benzofuran, benzothiofuran, indole, benzimidazole, benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole, and isoindazole.

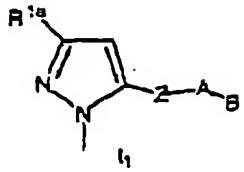
4. A compound according to Claim 3, wherein;

ring D is phenyl;

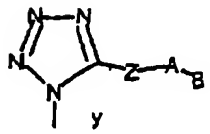
E is selected from F, Cl, Er, and OCH_3;

R is selected from H, F, Cl, and Br;

M is selected from the group:



and



A is selected from:

C_{5-6} carbocyclic residue substituted with 0-2 R^4, and
5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

Y is selected from one of the following carbocyclic and heterocyclic systems' which are substituted with 0-2 R^{4a}; phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, benzimidazolyl, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-tziazole, 1,2,5-triazole, and 1,3,4-triazole;

R^2, at each cccurrence, is selected from H, CF_3, C_{1-5} alkyl, benzyl, C_{5-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2a}, at each occurrence, is selected from H, CF_2, C_{1-6} alkyl, benzyl, phenethyl, C_{5-5} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{5-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{5-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a ring selected from imidazolyl, morpholino, piperazinyl, pyridyl, and pyrrolidinyl, substituted with 0-2 R^{4b};

R^4, at each occurrence, is selected from H, =O, OR^2, CH_2OR^2, F, Cl, C_{1-4} alkyl, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$, $CH(=NS(O)_2R^5)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $S(O)_2R^5$, and CF_3

provided that if B is H, then R^4 is other than tetrazole, C(O)-alkoxy, and $C(O)NR^2R^{2a}$;

R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, C_{1-4} alkyl, NR^2R^{2a}, $CH_2NR^2R^{2a}$, NR^2R^{2b}, $CH_2NR^2R^{2b}$, $(CH_2)_rC(O)R^{2c}$, $NR^3C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_2R^5$, and CF_3; and,

R^{4b}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$, F, Cl, C_{1-4} alkyl, NR^3R^{3a}, $CH_2NR^3R^{3a}$, $C(O)R^3$, $CH_2C(O)R^3$, $C(O)OR^{3c}$, $C(O)NR^3R^{3a}$, $CH(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_2CF_3$, $S(O)_2$-C_{1-4} alkyl, $S(O)_2$-phenyl, and CF_3.

5. A compound according to Claim 1, wherein compound is selected from:

3-Methyl-1-(2-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(3-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(2-hydroxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(3-hydroxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-hydroxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-bromo-4-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-iodo-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(3-methyl-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-carboxyldimethylamine)phenyl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-pyrrolidinocarbonyl)phenyl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-a-methyl-N-pyrrolidino)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-pyrrolidinocarbonyl)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-methanesulfonyl)phenyl)pyridin-2-yl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-N-pyrrolidinocarbonyl)pyridin-2-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-N-pyrrolidinocarbonyl)pyridin-2-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-sulfonamido)phenyl)pyridin-2-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-3-hydroxypyrrolidino)phenyl)carboxyamide;

1-(4-Methoxyphenyl)-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]tetrazole;

3-Methyl-1-(4-methoxy-3-chloro)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

3-Methyl-1-(4-trifluoromethoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(3-Bromophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl]carboxyamide;

1-(3-Iodophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(3,4-Methylenedioxanephenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4-Methoxyphenyl)-3-hydroxylmethylene-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide;

1-(4-Methoxyphenyl)-3-formaldehyde-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide;

1-(4-Methoxyphenyl)-3-methylcarboxylate-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide;

1-(4'-Chlorophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Chlorophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1-pyridyl-1'-phenyl]-4-yl)carboxyamide;

1-(3',4'-Dichlorophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(3'-Chlorophenyl)-3-methyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylthio)pyrazole-5-carboxamide;

1-(4-Methoxyphenyl)-3-(methylsulfonyl)-N-(5-(2'-methylsulfonylphenyl)pyrimid-2-yl)pyrazole-5-carboxamide;

N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazole-5-carboxamide;

N-(4-Benzoylpyrrolidine)-1-(4-methoxyphenyl)-3-(methylthio)-1H-pyrazole-5-carboxamide;

1-(4-Methoxyphenyl)-N-(5-(2'-methylsulfonylphenyl)pyrimid-2-yl)-3-(methylthio)-1H-pyrazole-5-carboxamide;

N-(4-Benzoylpyrrolidino)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazole-5-carboxamide;

N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methoxymethyl)-1H-pyrazole-5-carboxamide;

N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-carbomethoxy-1H-pyrazole-5-carboxamide;

N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylsulfonylmethyl)-1H-pyrazole-5-carboxamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-methanesulfonyl)phenyl)pyrimidin-2-yl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-2-carbomethoxypyrrolidino)phenyl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-3-aminopyrrolidino)phenyl)carboxyamide;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazole-5-N-(4-(N-carboxyl-3-methoxypyrrolidino)phenyl)carboxyamide;

3-Trifluoromathyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-aminosulfonyl)phenyl)pyridin-2-yl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-amidino)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-pyrrolidino)formylimino)phenyl)carboxya-

mide;

3-Trifluoromethyl-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))-1-(4-methoxyphenyl)pyrrolo[3,4-d]pyrazole-4,6-(1H,5H)-dione;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-carbomethoxy-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-hydoxymethyl-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-2-fluoro(4-(N-pyrrolidino)formylimino)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-pyrrolidino)formyl-N-((2-propyl)methylcarbamoyl)imino)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-pyrrolidino)formyl-N-(methanesulfamoyl)imino)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((4-amidino)phenyl)methyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((4-(N-pyrrolidino)formylimino)phenyl)methyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-[N-((1-benzyl)piperidin-4-yl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-((1-(pyridin-2-yl)methyl)piperidin-4-yl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(2-methylimidazo-1-yl))phenyl)carboxyamide;

3-Methyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(5-methylimidazol-1-yl}phenyl)carboxyamide;

3-Methyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(4-methylimidazol-1-yl}phenyl)carboxyamide ;

3-Trifluoromethyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(5-carbomethoxy-imidazol-1-yl}phenyl)carboxyamide;

3-Trifluoromethyl-(4-methoxy)phenyl-1H-pyrazole-5-(N-{4-(5-carboxy-imidazol-1-yl}phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-3-hydroxylmethyl-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-3-formaldehyde-1H-pyrazole-5-N-(4'-(pyrrolidinocarbonyl)phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-5-N-(4'-(pyrrolidinocarbonyl)anilide) 1H-pyrazol-3-yl-carboxylic acid;

1-(4'-Methoxyphenyl)-3-methylcarboxylate-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-3-cyanomethyl-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phenyl)carboxyamide;

2-(1'-(4"-Methoxyphenyl)-5'-(4"-pyrrolidinyl-one)anilide-1H-pyrazol-3'-yl)acetic acid;

1-(4'-Methoxyphenyl)-3-bromomethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Methoxyphenyl)-3-aminomethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Methoxyphenyl)-3-(N-methylsulfonylamino)methyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-

4-yl)carboxyamide;

1-(4'-Methoxyphenyl)-3-(imidazol-1-yl)methyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Methoxyphenyl)-3-hydroxylmethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Methoxyphenyl)-3-trifluoroacetylhydroxylmethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide;

1-(4'-Methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-methylsulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Methoxy-2'-hydroxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-methylsulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Methoxy-2'-methoxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Methoxy-2'-hydroxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-tert-butylaminosulfonyl-[1,1']-biphenyl)carboxyamide;

1-(4'-Methoxy-2'-hydroxycarbonylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Methoxy-2'-hydroxylmethylphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-(3"-methyl-3"-pyrazolin-5"-one-2"-yl)phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-(6"-methylbenzothiazol-2"-yl)phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-(4"-methylpiperidino)phenyl)carboxyamide;

1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazole-5-N-(4'-(2"-methylimidazol-1"-yl)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-carboxy(N-methylimidazo-2-yl)phenyl)carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-hydroxymethyl(2-(imidazol-2-yl)phenyl)))carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-hydroxymethyl(2-(1-benzyl-imidazol-2-yl)phenyl)))carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-(N-(4-(2-carboxy(imidazol-2-yl)phenyl)))carboxyamide;

3-Trifluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(N-(4-methoxyphenyl)amino-(2-thiazolyl)methyl)phenyl)))carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-(N-(4-(2-carboxy-(4,5-dihyrothiazol-2-yl)phenyl)))carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-4-(2-(4',5'-dihydro-1'H-imidazol-2'yl)phenyl)carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-[4-(1,4,5,6-tetrahydro-pyrimid-2-yl)-phenyl]carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-[4-(N-methyl-4,5,6-trihydro-pyrimid-2-yl)-phenyl]carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-1-(2-fluoro-4-imidazolinephenyl)carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-1-(2-fluoro-4-N-methylimidazolinephenyl)carboxyamide;

1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-[4-(4,5-dihydro-1-N-methyl-imidazo-2-yl)phenyl]carboxyamide;

1- (4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-N-[4-(pyrimidin-2-yl)phenyl]carboxyamide;

1-[(4-Methoxy)phenyl]-3-(ethoxycarbonyl)-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-(carboxyamide)-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(2-hydroxyethyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl) carboxyamide;

1-[(4-Methoxy)phenyl)-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide-3-hydroxamic acid;

1-[(4-Methoxy)phenyl]-3-[phenylcarboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl]carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(3-hydroxypropyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl) carboxyamide;

1-[(4-Methoxy)phenyl]-3-[methylcarboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1- [(4-Methoxy)phenyl]-3-[(benzyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(dimethyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(phenylethyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(2-hydroxyphenyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl) carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(3-hydroxyphenyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl) carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(4-hydroxyphenyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phenyl) carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(methoxycarbonyl)amino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-amino-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl)-3-[(methoxycarbonyl)methylamino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-

4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[(2-hydroxy)ethylamino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[E-2-(methoxycarbonyl)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[2-(methoxycarbonyl)ethyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[E-2-(carboxy)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[2-(carboxy)ethyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-[E-2-(carboxyamide)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide;

1- [(4-Methoxy)phenyl]-3- [E-2-(hydroxymethyl)ethenyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamide;

1- [(4-Methoxy)phenyl]-3- (3-hydroxypropyl)-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-propyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-cyano-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-(amidino)-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-(N-hydroxyamidino)-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide;

1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-4-(ethoxycarbonyl)-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide; and,

1-[(4-Methoxy)phenyl]-3-(trifluoromethyl)-1H-pyrazole-5-[(2'-methylsulfonyl-3-fluoro-[1,1']-biphen-4-yl)carboxyamide-4-carboxylic acid;

and pharmaceutically acceptable salts thereof.

6. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to one of Claims 1-5 or a pharmaceutically acceptable salt thereof.

7. A compound according to one of Claims 1-5 or a pharmaceutically acceptable salt thereof for use in therapy.

8. Use of a compound according to one of claims 1-5 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a thromboembolic disorder.

Patentansprüche

1. Verbindung der Formel I:

I

oder ein Stereoisomer oder pharmazeutisch akzeptables Salz davon, worin:

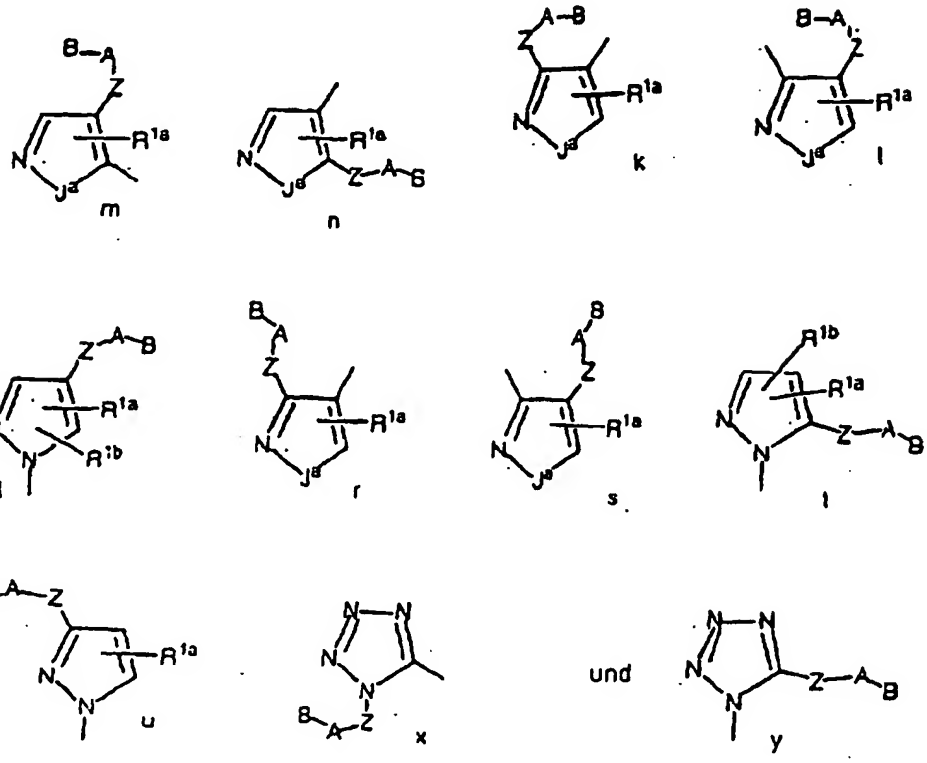
der Ring D für Phenyl oder Pyridyl steht;

E ausgewählt ist unter F, Cl, Br, I, OH, C_{1-3}-Alkoxy, SH, C_{1-3}-Alkyl-S, $S(O)R^{3b}$, $S(O)_2R^{3a}$, $S(O)_2NR^2R^{2a}$ und OCF_3;

R ausgewählt ist unter H, F, Cl, Br, I, OR^3, SR^3, NO_2 und CH_2OR^3;

E und R alternativ zusammen Methylendioxy oder Ethylandioxy bilden;

M ausgewählt ist unter:



J^a für NH oder NR^{1a} steht;

Z ausgewählt ist unter C_{1-4}-Alkylen, $(CH_2)_rO(CH_2)_r$, $(CH_2)_rNR^3(CH_2)_r$,$(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)O(CH_2)_r$, $(CH_2)_rOC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_rNR^3C(O)(CH_2)_r$, $(CH_2)_rOC(O)O(CH_2)_r$, $(CH_2)_rOC(O)NR^3(CH_2)_r$, $(CH_2)_rNR^3C(O)O(CH_2)_r$, $(CH_2)_rNR^3C(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, $(CH_2)_rSO_2NR^3(CH_2)_r$, $(CH_2)_rNR^3SO_2(CH_2)_r$, und $(CH_2)_rNR^3SO_2NR^3(CH_2)_r$, vorausgesetzt, dass Z keine N-N, N-O, N-S, NCH_2N, NCH_2O, oder NCH_2S-Bindung mit dem Ring M oder der Gruppe A bildet;

R^{1a} und R^{1b} unabhängig voneinander fehlen oder ausgewählt sind unter $-(CH_2)_r-R^{1'}$, $-CH=CH-R^{1'}$, NCH_2R^{1*}, OCH_2R^{1*}, SCH_2R^{1*}, $NH(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$, und $S(CH_2)_2(CH_2)_tR^{1'}$;

R^{1a} und R^{1b}, alternativ, wenn sie an benachbarte Kohlenstoffatome gebunden sind, zusammen mit den Atomen, an die sie gebunden sind, einen 5-8-gliedrigen gesättigten, teilweise gesättigten oder ungesättigten Ring bilden, der mit 0-2 R^4 substituiert ist und 0-2 Heteroatome enthält, die ausgewählt sind unter N, O, und S;

wenn Z für C(O)NH steht und R^{1a} an ein Z benachbartes Ringkohlenstoffatom gebunden ist, R^{1a} alternativ für C(O) steht, das den Amidwasserstoff von Z ersetzt, wobei ein cyclisches Imid gebildet wird;

$R^{1'}$ ausgewählt ist unter H, C_{1-3}-Alkyl, F, Cl, Br, I, -CN, -CHO, $(CF_2)_rCF_3$, $(CH_2)_rOR^2$,NR^2R^{2a}, $C(O)R^{2c}$, $OC(O)R^2$, $(CF_2)_rCO_2R^{2c}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $CH(=NR^{2c})NR^2R^{2a}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^{2b}$,$NR^2C(O)_2R^{2a}$, $OC(O)NR^{2a}R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$, $NR^2SO_2R^{2b}$, einem carbocyclischen C_{3-6}-Rest, der mit 0-2 R^4 substituiert ist und einem 5-10-gliedrigen heterocyclischen System, das 1-4 Heteroatome aufweist, die ausgewählt sind unter N, O und S, und das mit 0-2 R^4 substituiert ist;

R^{1*} ausgewählt ist unter $H,CH(CH_2OR^2)_2$, $C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $S(O)R^{2b}$, $S(O)_2R^{2b}$, und $SO_2NR^2R^{2a}$;

jedes R^2 ausgewählt ist unter H,CF_3, C_{1-6}-Alkyl, Benzyl, einem carbocyclischen C_{3-6}-Rest, der mit 0-2 R^{4b} substituiert ist und einem 5-6-gliedrigen heterocyclischen System, das 1-4 Heteroatome aufweist, die ausgewählt sind unter N, O und S und das mit 0-2 R^{4b} substituiert ist;

jedes R^{2a} ausgewählt ist unter H, CF_3, C_{1-6}-Alkyl, Benzyl, Phenethyl, einem carbocyclischen C_{3-6}-Rest, der mit 0-2 R^{4b} substituiert ist und einem 5-6-gliedrigen heterocyclischen System, das 1-4 Heteroatome aufweist, die ausgewählt sind unter N, O und S und das mit 0-2 R^{4b} substituiert ist;

jedes R^{2b} ausgewählt ist unter CF_3, C_{1-4}-Alkoxy, C_{1-6}-Alkyl, Benzyl, einem carbocyclischen C_{3-6}-Rest, der mit 0-2 R^{4b} substituiert ist und einem 5-6-gliedrigen heterocyclischen System, das 1-4 Heteroatome aufweist, die ausgewählt sind unter N, O und S und das mit 0-2 R^{4b} substituiert ist;

jedes R^{2c} ausgewählt ist unter CF_3, OH, C_{1-4}-Alkoxy, C_{1-6}-Alkyl, Benzyl, einem carbocyclischen C_{3-6}-Rest, der mit 0-2 R^{4b} substituiert ist und einem 5-6-gliedrigen heterocyclischen System, das 1-4 Heteroatome aufweist, die ausgewählt sind unter N, O und S, und das mit 0-2 R^{4b} substituiert ist;

R^2 und R^{2a} alternativ zusammen mit dem Atom, an das sie gebunden sind, einen 5- or 6-gliedrigen gesättigten, teilweise gesättigten oder ungesättigten Ring bilden, der mit 0-2 R^{4b} substituiert ist und 0-1 weitere Heteroatome enthält, die ausgewählt sind unter N, O und S;

jedes R^3 ausgewählt ist unter H, C_{1-4}-Alkyl und Phenyl;

jedes R^{3a} ausgewählt ist unter H, C_{1-4}-Alkyl und Phenyl;

jedes R^{3b} ausgewählt ist unter H, C_{1-4}-Alkyl und Phenyl;

jedes R^{3c} ausgewählt ist unter C_{1-4}-Alkyl und Phenyl;

A ausgewählt ist unter:

einem carbocyclischen C_{3-10}-Rest, der mit 0-2 R^4 substituiert ist und
einem 5-10-gliedrigen heterocyclicschen System, das 1-4 Heteroatome aufweist, die ausgewählt sind unter N, O und S, und das mit 0-2 R^4 substituiert ist;

B ausgewählt ist unter Y und X-Y;

X ausgewählt ist unter C_{1-4}-Alkylen, $-CR^2(CR^2R^{2b})(CH_2)_t-$, -C(O)-, $-C(=NR^*)-$, $-CR^2(NR^{1*}R^2)-$, $-CR^2(OR^2)-$, $-CR^2(SR^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-S(O)_p-$, $-S(O)_pCR^2R^{2a}-$, $-CR^2R^{2a}S(O)_p-$, $-S(O)_2NR^2-$, $-NR^2S(O)_2-$, $-NR^2S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S(O)_2NR^2-$, $-NR^2S(O)_2NR^2-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $NR^2C(O)O-$, $-OC(O)NR^2-$, $-NR^2C(O)NR^2-$, $-NR^2-$,

$-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$ und $-OCR^2R^{2a}-$;

Y ausgewählt ist unter:

$(CH_2)_rNR^2R^{2a}$, vorausgesetzt, dass X-Y keine N-N, O-N oder S-N-Bindung bildet,

einem carbocyclischen C_{3-10}-Rest, der mit 0-2 R^{4a} substituiert ist und

einem 5-10-gliedrigen heterocyclischen System, das 1-4 Heteroatome aufweist, die ausgewählt sind unter N, O und S, und das mit 0-2 R^{4a} substituiert ist;

jedes R^4 ausgewählt ist unter H, =O, $(CH_2)_rOR^2$, F,

Cl, Br, I, C_{1-4}-Alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$,$NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$, $CH(=NS(O)_2R^5)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, C (O)NHC $(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4}-Alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, $(CF_2)_rCF_3$, $NCH_2R^{1''}$, $OCH_2R^{1''}$, $SCH_2R^{1''}N(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$ und $S(CH_2)_2(CH_2)_tR^{1'}$;

alternativ ein R^4 einen 5-6-gliedrigen aromatischen Heterocyclus bedeutet, der 1-4 Heteroatome aufweist, die ausgewählt sind unter N, O und S;

jedes R^{4a} ausgewählt ist unter H, =O, $(CH_2)_rOR^2$, $(CH_2)_r$-F, $(CH_2)_r$-Br, $(CH_2)_r$-Cl, I, C_{1-4}-Alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rNR^2R^{2b}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2- C_{1-4}-Alkyl, $C(O)NHSO_2$-C_{1-4}-Alkyl, $NR^2SO_2R^5$, S(O)pR^5, und $(CF_2)_rCF_3$;

alternativ ein R^{4a} einen 5-6-gliedrigen aromatischen Heterocyclus bedeutet, der 1-4 Heteroatome aufweist, die ausgewählt sind unter N, O und S und der mit 0-1 R^5 substituiert ist;

jedes R^{4b} ausgewählt ist unter H, =O,$(CH_2)_rOR^3$, F, Cl, Br, I, C_{1-4}-Alkyl, -CN, NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^3C$,$NR^{3c}(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $CH(=NR^3)NR^3R^{3a}$,$NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4}-Alkyl, $NR^3SO_2CF_3$, NR^3SO_2-Phenyl, $S(O)_pCF_3$, $S(O)_p$-C_{1-4}-Alkyl,, $S(O)_p$-Phenyl, und $(CF_2)_rCF_3$;

jedes R^5 ausgewählt ist unter CF_3, C_{1-6}-Alkyl, Phenyl, das mit 0-2 R^6 substituiert ist und Benzyl, das mit 0-2 R^6 substituiert ist;

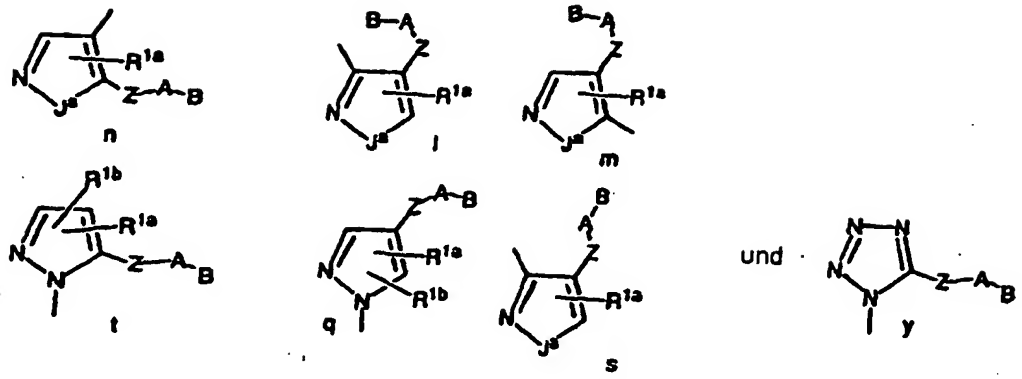
jedes R^6 ausgewählt ist unter H, OH, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4}-Alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, und NR^2SO_2 C_{1-4}-Alkyl;

p ausgewählt ist unter 0, 1 und 2;

r ausgewählt ist unter 0, 1, 2 und 3; und

t ausgewählt ist unter 0 und 1.

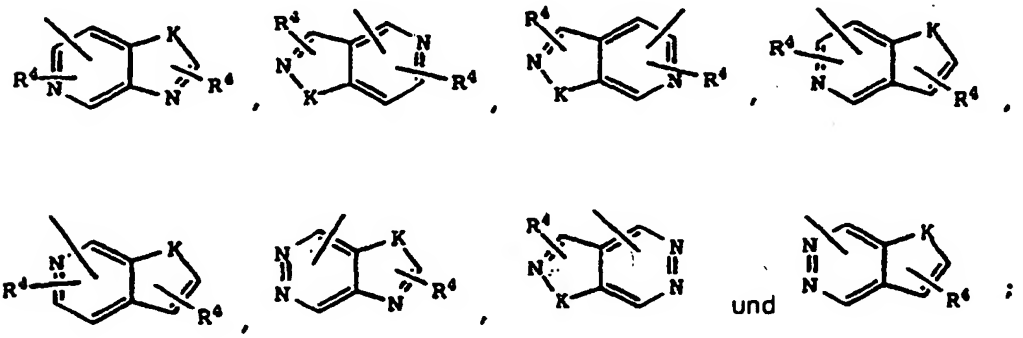
2. Verbindung nach Anspruch 1, worin M ausgewählt ist unter :



Z ausgewählt ist unter $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)O(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, und $(CH_2)_rSO_2NR^3(CH_2)_r$; und

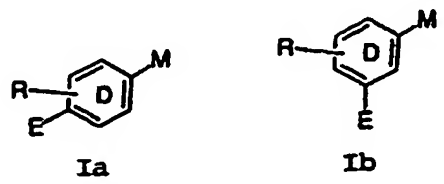
Y ausgewählt ist unter einem der folgenden carbocyclischen und heterocyclischen Systeme, die mit 0-2 R^{4a} substituiert sind; Phenyl, Piperidinyl, Piperazinyl, Pyridyl, Pyrimidyl, Furanyl, Morpholinyl, Thiophenyl, Pyrrolyl, Pyrrolidinyl, Oxazolyl, Isoxazolyl, Thiazolyl, Isothiazolyl, Pyrazolyl, Imidazolyl, Oxadiazol, Thiadiazol, Triazol, 1,2,3-Oxadiazol, 1,2,4-Oxadiazol, 1,2,5-Oxadiazol, 1,3,4-Oxadiazol, 1,2,3-Thiadiazol, 1,2,4-Thiadiazol, 1,2,5-Thiadiazol, 1,3,4-Thiadiazol, 1,2,3-Triazol, 1,2,4-Triazol, 1,2,5-Triazol, 1,3,4-Triazol, Benzofuran, Benzothiofuran, Indol, Benzimidazol, Benzoxazol, Benzthiazol, Indazol, Benzisoxazol, Benzisothiazol und Isoindazol;

Y auch ausgewählt sein kann unter den folgenden bicyclischen Heteroaryl-Ringsystemen:



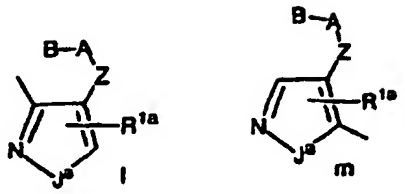
K ausgewählt ist unter O, S, NH und N.

3. Verbindung nach Anspruch 2, wobei die Verbindung der Formel Ia oder Ib entspricht:



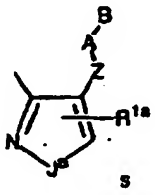
worin:

Ring D für Phenyl oder Pyridyl steht;
E ausgewählt ist unter F, Cl, Br, and C_{1-3}-Alkoxy;
R ausgewählt ist unter H, F, Cl, Br, OR^3 und CH_2OR^3;
M ausgewählt ist unter:

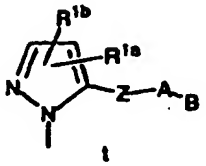


l

m

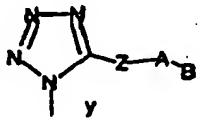


s



t

und



y

Z ausgewählt ist unter $(CH_2)_rC(O)(CH_2)_r$ und $(CH_2)_rC(O)NR^3(CH_2)_r$; und,
Y ausgewählt ist unter einem der folgenden carbocyclischen und heterocyclischen Systeme, die mit 0-2 R^{4a} substituiert sind; Phenyl, Piperidinyl, Piperazinyl, Pyridyl, Pyrimidyl, Furanyl, Morpholinyl, Thiophenyl, Pyrrolyl, Pyrrolidinyl, Oxazolyl, Isoxazolyl, Thiazolyl, Isothiazolyl, Pyrazolyl, Imidazolyl, Oxadiazol, Thiadiazol, Triazol, 1,2,3-Oxadiazol, 1,2,4-Oxadiazol, 1,2,5-Oxadiazol, 1,3,4-Oxadiazol, 1,2,3-Thiadiazol,1,2,4-Thiadiazol, 1,2,5-Thiadiazol, 1,3,4-Thiadiazol, 1,2,3-Triazol, 1,2,4-Triazol, 1,2,5-Triazol,1,3,4-Triazol, Benzofuran, Benzothiofuran, Indol, Benzimidazol, Benzoxazol, Benzthiazol, Indazol, Benzisoxazol, Benzisothiazol und Isoindazol.

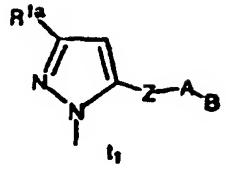
4. Verbindung nach Anspruch 3, worin:

Ring D für Phenyl steht;

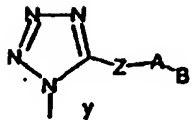
E ausgewählt ist unter F, Cl, Br und OCH_3;

R ausgewählt ist unter H, F, Cl, and Br,

M ausgewählt ist unter



und



A ausgewählt ist unter:

einem carbocyclischen C_{5-6}-Rest, der mit 0-2 R^4 substituiert ist und
einem 5-6-gliedrigen heterocyclischen System, das 1-4 Heteroatome aufweist, die ausgewählt sind unter N, O und S, und das mit 0-2 R^4 substituiert ist;

Y ausgewählt ist unter einem der folgenden carbocyclischen und heterocyclischen Systeme, die mit 0-2 R^{4a} substituiert sind; Phenyl, Piperidinyl, Piperazinyl, Pyridyl, Pyrimidyl, Furanyl, Morpholinyl, Thiophenyl, Pyrrolyl, Pyrrolidinyl, Oxazolyl, Isoxazolyl, Thiazolyl, Isothiazolyl, Pyrazolyl, Imidazolyl, Benzimidazolyl, Oxadiazol, Thiadiazol, Triazol, 1,2,3-Oxadiazol, 1,2,4-Oxadiazol, 1,2,5-Oxadiazol, 1,3,4-Oxadiazol, 1,2,3-Thiadiazol, 1,2,4-Thiadiazol, 1,2,5-Thiadiazol, 1,3,4-Thiadiazol, 1,2,3-Triazol, 1,2,4-Triazol, 1,2,5-Triazol und 1,3,4-Triazol;

jedes R^2 ausgewählt ist unter H, CF_3,C_{1-6}-Alkyl, Benzyl, einem carbocyclischen C_{5-6}-Rest, der mit 0-2 R^{4b} substituiert ist und einem 5-6-gliedrigen heterocyclischen System, das 1-4 Heteroatome aufweist, die ausgewählt sind unter N, O und S, und das mit 0-2 R^{4b} substituiert ist;

jedes R^{2a} ausgewählt ist unter H, CF_3,C_{1-6}-Alkyl, Benzyl, Phenethyl, einem carbocyclischen C_{5-6}-Rest, der mit 0-2 R^{4b} substituiert ist und einem 5-6-gliedrigen heterocyclischen System, das 1-4 Heteroatome enthält, die ausgewählt sind unter N, O und S, und das mit 0-2 R^{4b} substituiert ist;

jedes R^{2b} ausgewählt ist unter CF_3, C_{1-4}-Alkoxy, C_{1-6}-Alkyl, Benzyl einem carbocyclischen C_{5-6}-Rest, der mit 0-2 R^{4b} substituiert ist und einem 5-6-gliedrigen heterocyclischen System, das 1-4 Heteroatome enthält, die ausgewählt sind unter N, O und S, und das mit 0-2 R^{4b} substituiert ist;

jedes R^{2c} ausgewählt ist unter CF_3, OH, C_{1-4}-Alkoxy, C_{1-6}-Alkyl, Benzyl einem carbocyclischen C_{5-6}-Rest, der mit 0-2 R^{4b} substituiert ist und einem 5-6-gliedrigen heterocyclischen System, das 1-4 Heteroatome enthält, die ausgewählt sind unter N, O und S, und das mit 0-2 R^{4b} substituiert ist;

R^2 und R^{2a} alternativ zusammen mit dem Atom, an das sie gebunden sind, einen Ring bilden, der ausgewählt ist unter Imidazolyl, Morpholino, Piperazinyl, Pyridyl und Pyrrolidinyl, substituiert mit 0-2 R^{4b};

jedes R^4 ausgewählt ist unter H, =O, OR^2, CH_2OR^2, F, Cl, C_{1-4}-Alkyl, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$,$CH(=NS(O)_2R^5)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4}-Alkyl, $S(O)_2R^5$ und CF_3,

unter der Voraussetzung, dass, wenn B für H steht, R^4 eine andere Bedeutung hat als Tetrazol, C(O)-Alkoxy und $C(O)NR^2R^{2a}$;

jedes R^{4a} ausgewählt ist unter H, =O, $(CH_2)_rOR^2$, F, Cl, C_{1-4}-Alkyl, NR^2R^{2a},$CH_2NR^2R^{2a}$, NR^2R^{2b}, $CH_2NR^2R^{2b}$,

$(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_2R^5$ und CF_3; und

jedes R^{4b} ausgewählt ist unter H, =O,$(CH_2)_rOR^3$, F, Cl, C_{1-4}-Alkyl, NR^3R^{3a}, $CH_2NR^3R^{3a}$, $C(O)R^3$, $CH_2C(O)R^3$, $C(O)OR^{3c}$, $C(O)NR^3R^{3a}$, $CH(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4}-Alkyl, $NR^3SO_2CF_3$, NR^3SO_2-Phenyl, $S(O)_2CF_3$, $S(O)_2$-C_{1-4}-Alkyl, $S(O)_2$-Phenyl und CF_3.

5. Verbindung nach Anspruch 1, wobei die Verbindung ausgewählt ist unter:

3-Methyl-1-(2-methoxy)phenyl-1H-pyrazol-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
3-Methyl-1-(3-methoxy)phenyl-1H-pyrazol-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
3-Methyl-1-(4-methoxy)phenyl-1H-pyrazol-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
3-Methyl-1-(2-hydroxy)phenyl-1H-pyrazol-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
3-Methyl-1-(3-hydroxy)phenyl-1 H-pyrazol-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
3-Methyl-1-(4-hydroxy)phenyl-1H-pyrazol-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
3-Methyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(3-fluor-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
3-Methyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(3-brom-4-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
3-Methyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(3-iod-(2'-aminosulfonyl-[1,1]-biphen-4-yl)carboxyamid;
3-Methyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(3-methyl-(2'aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
3-Methyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(4-N-carboxyldimethylamin)phenyl)carboxyamid;
3-Methyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(4-N-pyrrolidinocarbonyl)phenyl)carboxyamid;
3-Methyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(4-a-methyl-N-pyrrolidino)phenyl)carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(2'aminosulfonyl- [1,1']-biphen-4-yl)carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(4-N-pyrrolidinocarbonyl)phenyl)carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(5-(2-methansulfonyl)phenyl)pyridin-2-yl)carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(5-N-pyrrolidinocarbonyl)pyridin-2-yl)carboxyamid;
3-Methyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(5-N-pyrrolidinocarbonyl)pyridin-2-yl)carboxyamid;
3-Methyl-1-(4-methoxyphenyl)-1H-pyrazot-5-(N-(5-(2-sulfonamido)phenyl)pyridin-2-yl)carboxyamid;
3-Methyl-1-(4-methoxyphenyl)-1H-pyrazol-5-N-(4-(N-carboxyl-3-hydroxypyrrolidino)phenyl)carboxyamid;
1-(4-Methoxyphenyl)-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]tetrazol;
3-Methyl-1-(4-methoxy-3-chlor)phenyl-1H-pyrazol-5-(N-(2'aminosulfonyl- [1,1']-biphen-4-yl)carboxyamid;
3-Methyl-1-(4-trifluormethoxy)phenyl-1H-pyrazol-5-(N-(2'aminosulfonyl- [1,1']-biphen-4-yl)carboxyamid;
1-(3-Bromphenyl)-3-methyl-1H-pyrazol-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-(3-Iodphenyl)-3-methyl-1H-pyrazol-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-(3,4-Methylendioxanphenyl)-3-methyl-1H-pyrazol-5-[(2'aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-(4-Methoxyphenyl)-3-hydroxylmethylen-1H-pyrazol-5-(4-pyrrolidinocarbonyl)anilid;
1-(4-Methoxyphenyl)-3-formaldehyd-1H-pyrazol-5-(4'pyrrolidinocarbonyl)anilid;
1-(4-Methoxyphenyl)-3-methylcarboxylate-1H-pyrazol-5-(4-pyrrolidinocarbonyl)anilid;
1-(4'-Chlorphenyl)-3-methyl-1 H-pyrazol-5-[(2'-aminosulfonyl [1,1']-biphenyl-4-yl)carboxyamid;
1-(4'-Chlorphenyl)-3-methyl-1H-pyrazol-5-[(2'-aminosulfonyl-[1-pyridyl-1'-phenyl]-4-yl)carboxyamid;
1-(3',4'-Dichlorphenyl)-3-methyl-1H-pyrazol-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-(3'-Chlorphenyl)-3-methyl-1 H-pyrazol-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylthio)pyrazol-5-carboxamid;
1-(4-Methoxyphenyl)-3-(methylsulfonyl)-N-(5-(2'methylsulfonylphenyl)pyrimid-2-yl)pyrazol-5-carboxamid;
N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylsulfonyl) -1 H-pyrazol-5-carboxamid;
N-(4-Benzoylpyrrolidino)-1-(4-methoxyphenyl)-3-(methylthio)-1H-pyrazol-5-carboxamid;
1-(4-Methoxyphenyl)-N-(5-(2'-methylsulfonylphenyl)pyrimid-2-yl)-3-(methylthio)-1H-pyrazol-5-carboxamid;
N-(4-Benzoylpyrrolidino)-1-(4-methoxyphenyl)-(3-methylsulfonyl)-1H-pyrazol-5-carboxamid;
N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methoxymethyl)-1H-pyrazol-5-carboxamid;
N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-carbomethoxy-1H-pyrazol-5-carboxamid;
N-(2'-Aminosulfonyl-[1,1']-biphen-4-yl)-1-(4-methoxyphenyl)-3-(methylsulfonylmethyl)-1H-pyrazol-5-carboxamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazot-5-(N-(5-(2-methansulfonyl)phenyl)pyrimidin-2-yl)carboxyamid;
3-Methyl-1-(4-methoxyphenyl)-1H-pyrazot-5-N-(4-(N-carboxy)-2-carbomethoxypyrrolidino) phenyl) carboxyamid;
3-Methyl-1-(4-methoxyphenyl)-1H-pyrazol-5-N-(4-(N-carboxyl-3-aminopyrrolidino)phenyl)carboxyamid;

3-Methyl-1-(4-methoxyphenyl)-1H-pyrazol-5-N-(4-(N-carboxyl-3-methoxypyrrolidino)phenyl)carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(5-(2-aminosulfonyl)phenyl) pyridin-2 -yl)carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(4-amidino) phenyl)carboxyamid;
3-Trifluormethyl-l-(4-methoxyphenyl)-1H-pyrazol-5-(N-(4-(Npyrrolidino)formylimino)phenyl)carboxyamid;
3-Trifluormethyl-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))-1-(4-methoxyphenyl)pyrrolo[3,4-d]pyrazol-4,6-(1H, 5H)-dion;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-carbomethoxy-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)) carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-hydroxymethyl-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)) carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-2-fluor(4-(N-pyrrolidino)formylimino)phenyl)carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(4-(Npyrrolidino)formyl-N-((2-propyl)methylcarbamoyl)imino)phenyl)carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(4-(Npyrrolidino)formyl-N-(methansulfamoyl)imino) phenyl)carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-((4-amidino)phenyl)methyl)carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-((4-(Npyrrolidino)formylimino)phenyl)methyl)carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-((1-benzyl)piperidin-4-yl)carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-((1-(pyridin-2-yl)methyl)piperidin-4-yl)carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(4-(2-methylimidazo-1-yl))phenyl)carboxyamid;
3-Methyl-(4-methoxy)phenyl-1 H-pyrazol-5-(N-{4-(5-methylimidazol-1-yl)phenyl)carboxyamid;
3-Methyl-(4-methoxy)phenyl-1 H-pyrazol-5-(N-{4-(4-methyl-imidazol-1-yl)phenyl)carboxyamid;
3-Trifluormethyl-(4-methoxy)phenyl-1H-pyrazol-5-(N-{4-(5-carbomethoxy-imidazol-1-yl}phenyl)carboxyamid;
3-Trifluormethyl-(4-methoxy)phenyl-1H-pyrazol-5-(N-{4-(5-carboxy-imidazol-1-yl)phenyl)carboxyamid;
1-(4'-Methoxyphenyl)-3-hydroxylmethyl-1H-pyrazol-5-N-(4'pyrrolidinocarbonyl)phenyl)carboxyamid;
1-(4'-Methoxyphenyl)-3-formaldehyd-1H-pyrazol-5-N-(4'-(pyrrolidinocarbonyl)phenyl)carboxyamid;
1-(4'-Methoxyphenyl)-5-N-(4'-(pyrrolidinocarbonyl)anilid)-1Hpyrazol-3-yl-carbonsäure;
1-(4'-Methoxyphenyl)-3-methylcarboxylat-1H-pyrazol-5-N-(4'pyrrolidinocarbonyl) phenyl)carboxyamid;
1-(4'-Methoxyphenyl)-3-cyanomethyl-1H-pyrazol-5-N-(4'pyrrolidinocarbonyl)phenyl)carboxyamid;
2-(1'-(4"-Methoxyphenyl)-5'-(4'-pyrrolidinyl-on)anitid-1Hpyrazol-3'-yl)essigsäure;
1-(4'-Methoxyphenyl)-3-brommethyl-1H-pyrazol-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-(4'-Methoxyphenyl)-3-aminomethyl-1H-pyrazol-5-N-(2'aminosulfonyl- [1,1']-biphen-4-yl) carboxyamid;
1-(4'-Methoxyphenyl)-3-(N-methylsulfonylamino)methyl-1Hpyrazol-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamid;
1-(4'-Methoxyphenyl)-3-(imidazol-1-yl)methyl-1H-pyrazol-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1- (4'-Methoxyphenyl)-3-hydroxylmethyl-1H-pyrazol-5-N-(2'aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-(4'-Methoxyphenyl)-3-trifluoracetylhydroxylmethyl-1Hpyrazol-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-(4'-Methoxy-2'-methoxycarbonylphenyl)-3-trifluormethyl-1Hpyrazol-5-N-(2'-methylsulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-(4'-Methoxy-2'-hydroxycarbonylphenyl)-3-trifluormethyl-1Hpyrazol-5-N-(2'-methylsulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-(4'-Methoxy-2'-methoxycarbonylphenyl)-3-trifluormethyl-1Hpyrazol-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-(4'-Methoxy-2'-hydroxycarbonylphenyl)-3-trifluormethyl-1Hpyrazol-5-N-(2'-tert-butylaminosulfonyl-[1,1']-biphenyl)carboxyamid;
1-(4'-Methoxy-2'-hydroxycarbonylphenyl)-3-trifluormethyl-1Hpyrazol-5-N- (2' -aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-(4'-Methoxy-2'-hydroxylmethylphenyl)-3-trifluormethyl-1Hpyrazol-5-N-(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamid;
1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazol-5-N-(4'-(3"-methyl-3"-pyrazolin-5"on-2"-yl)phenyl)carboxyamid;
1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazol-5-N-(4'-(6"methylbenzothiazol-2"-yl)phenyl)carboxyamid;
1-(4'-Methoxyphenyl)-3-methyl-1H-pyrazol-5-N-(4'-(4"methylpiperidino)phenyl)carboxyamid;
1-(4'-Methoxyphenyl)-3-methyl-1 H-pyrazol-5-N-(4'-(2"methylimidazol-1"-yl)phenyl)carboxyamid;

3-Trifluormethyl-1-(4-methoxyphenyl)-1H -pyrazol-5- (N- (4-carboxy(N-methylimidazo-2-yl)phenyl)carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(4-hydroxymethyl(2-(imidazol-2-yl)phyenyl)))carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(4-hydroxyrnethyl(2-(1-benzyl-imidazol-2-yl)phenyl)))carboxyamid;
1-(4-Methoxyphenyl)-3-trifluormethyl-1H-pyrazol-5-(N-(4-(2-carboxy(imidazol-2-yl)phenyl)))carboxyamid;
3-Trifluormethyl-1-(4-methoxyphenyl)-1H-pyrazol-5-(N-(4-(N-(4-methoxyphenyl)amino-(thiazolyl)methyl)phenyl)))carboxyamid;
1-(4-Methoxyphenyl)-3-trifluormethyl-1H-pyrazol-5-(N-(4-(2-carboxy-(4,5-dihydrothiazol-2-yl)phenyl)))carboxyamid;
1-(4-Methoxyphenyl)-3-trifluormethyl-1H-pyrazol-5-N-4-(2-(4',5'-dihydro-1'H-imidazol-2'-yl)phenyl)carboxyamid;
1-(4-Methoxyphenyl)-3-trifluormethyl-1H-pyrazol-5-[4-(1,4,5,6-tetrahydro-pyrimid-2-yl)-phenyl]carboxyamid;
1-(4-Methoxyphenyl)-3-trifluormethyl-1H-pyrazol-5-[4-(Nmethyl-4,5,6-trihydro-pyrimid-2-yl)-phenyl]carboxyamid;
1-(4-Methoxyphenyl)-3-trifluormethyl-1H-pyrazol-5-N-1-(2-fluor-4-imidazolinphenyl)carboxyamid;
1-(4-Methoxyphenyl)-3-trifluormethyl-1H-pyrazol-5-N-1-(2-fluor-4-N-methylimidazolinphenyl)carboxyamid;
1-(4-Methoxyphenyl)-3-trifluormethyl-1H-pyrazol-5-N-[4-(4,5-dihydro-1-N-methyl-imidazo-2-yl)phenyl]carboxyamid;
1-(4-Methoxyphenyl)-3-trifluormethyl-1H-pyrazol-5-N-[4-(pyrimidin-2-yl)phenyl]carboxyamid;
1-[(4-Methoxy)phenyl]-3-(ethoxycarbonyl)-1H-pyrazol-5-[(4-(Npyrrolidinocarbonyl)phenyl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-(carboxyamid)-1H-pyrazol-5-[(4-(Npyrrolidinocarbonyl)phenyl) carboxyamid;
1-[(4-Methoxy)phenyl]-3-[(2-hydroxyethyl)carboxyamid]-1Hpyrazol-5- [(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamid;
1-[(4-Methoxy)phenyl]-1H-pyrazol-5-[(4-(pyrrolidinocarbonyl)phenyl)-carboxyamid-3-hydroxamsäure;
1-[(4-Methoxy)phenyl]-3-[phenylcarboxyamid]-1H-pyrazol-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-[(3-hydroxypropyl)carboxyamid]-1Hpyrazol-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-[methylcarboxyamid]-1H-pyrazol-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-[(benzyl)carboxyamid]-1H-pyrazol-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-[(dimethyl)carboxyamid]-1H-pyrazol-5-[(4-(Npyrrolidinocarbonyl)phenyl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-[(phenylethyl)carboxyamid]-1Hpyrazol-5-[(4-(N-pyrrolidinocarbonyl)phenyl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-[(2-hydroxyphenyl)carboxyamid]-1Hpyrazol-5-[(4-(N-pyrrolidinocarbonyl)phenyl) carboxyamid;
1-[(4-Methoxy)phenyl]-3-[(3-hydroxyphenyl)carboxyamid]-1Hpyrazol-5-[(4-(N-pyrrolidinocarbonyl)phenyl) carboxyamid;
1-[(4-Methoxy)phenyl]-3-[(4-hydroxyphenyl)carboxyamid]-1Hpyrazol-5-[(4-(N-pyrrolidinocarbonyl)phenyl) carboxyamid;
1-[(4-Methoxy)phenyl]-3-[(methoxycarbonyl)amino]-1H-pyrazol-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-amino-1H-pyrazol-5-[(2'aminosulfonyl-[1,1']-biphen-4-yl) carboxyamid;
1-[(4-Methoxy)phenyl]-3-[(methoxycarbonyl)methylamino]-1Hpyrazol-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl) carboxyamid;
1-[(4-Methoxy)phenyl]-3-[(2-hydroxy)ethylamino]-1H-pyrazol-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-[E-2-(methoxycarbonyl)ethenyl]-1Hpyrazol-5-[(2'-aminosulfonyl-[1, 1']-biphen-4-yl) carboxyamid;
1-[(4-Methoxy)phenyl]-3-[2-(methoxycarbonyl)ethyl]-1Hpyrazol-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-[E-2-(carboxy)ethenyl]-1H-pyrazol-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-[2-(carboxy)ethyl]-1H-pyrazol-5-[(2'aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-[E-2-(carboxyamid)ethenyl]-1H-pyrazol-5-[(2'aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;

1-[(4-Methoxy)phenyl]-3-[E-2-(hydroxymethyl)ethenyl]-1Hpyrazol-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-(3-hydroxypropyl)-1H-pyrazol-5-[(2'aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-propyl-1H-pyrazol-5-[(2'aminosulfonyl-[1,1']-biphen-4-yl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-(trifluormethyl)-4-cyano-1H-pyrazol-5-[(2'-methylsulfonyl-3-fluor-[1,1']-biphen-4-yl) carboxyamid;
1-[(4-Methoxy)phenyl]-3-(trifluormethyl)-4-(amidino)-1Hpyrazol-5-[(2'-methylsulfonyl-3-fluor-[1,1']-biphen-4-yl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-(trifluormethyl)-4-(N-hydroxyamidino)-1H-pyrazol-5-[(2'-methylsulfonyl-3-fluor-[1,1']-biphen-4-yl)carboxyamid;
1-[(4-Methoxy)phenyl]-3-(trifluormethyl)-4-(ethoxycarbonyl)-1H-pyrazol-5-[(2'methylsulfonyl-3-fluor-[1,1']-biphen-4-yl)carboxyamid; und
1-[(4-Methoxy)phenyl]-3-(trifluormethyl)-1H-pyrazol-5-[(2'-methylsulfonyl-3-fluor-[1,1']-biphen-4-yl)carboxyamid-4-carbonsäure;

und den pharmazeutisch akzeptablen Salzen davon.

6. Pharmazeutische Zusammensetzung, umfassend:

einen pharmazeutisch akzeptablen Träger und eine therapeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 5 oder ein pharmazeutisch akzeptables Salz davon.

7. Verbindung nach einem der Ansprüche 1 bis 5 oder ein pharmazeutisch akzeptables Salz davon zur Verwendung in der Therapie.

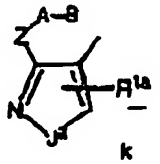
8. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 5 oder ein pharmazeutisch akzeptables Salz davon zur Herstellung eines Medikaments zur Behandlung einer thromboembolischen Störung.

Revendications

1. Composé de formule I :

I

ou l'un de ses stéréoisomères ou l'une de ses formes salifiées acceptables pharmaceutiquement ; dans lequel
le cycle D est phényle ou pyridyle ;
E est choisi parmi F, Cl, Br, I, OH, alcoxy ayant de 1 à 3 atomes de carbone, SH, alcoyle-S ayant de 1 à 3 atomes de carbone, $S(O)R^{3b}$, $S(O)_2R^{3a}$, $S(O)_2NR^2R^{2a}$, et OCF_3 ;
R est choisi parmi H, F, Cl, Br, I, OR^3, SR^3, NO_2 et CH_2OR^3 ;
en variante, E et R se combinent pour former un méthylènedioxy ou un éthylènedioxy ;
M est choisi dans le groupe :



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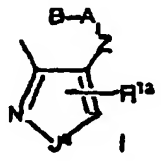

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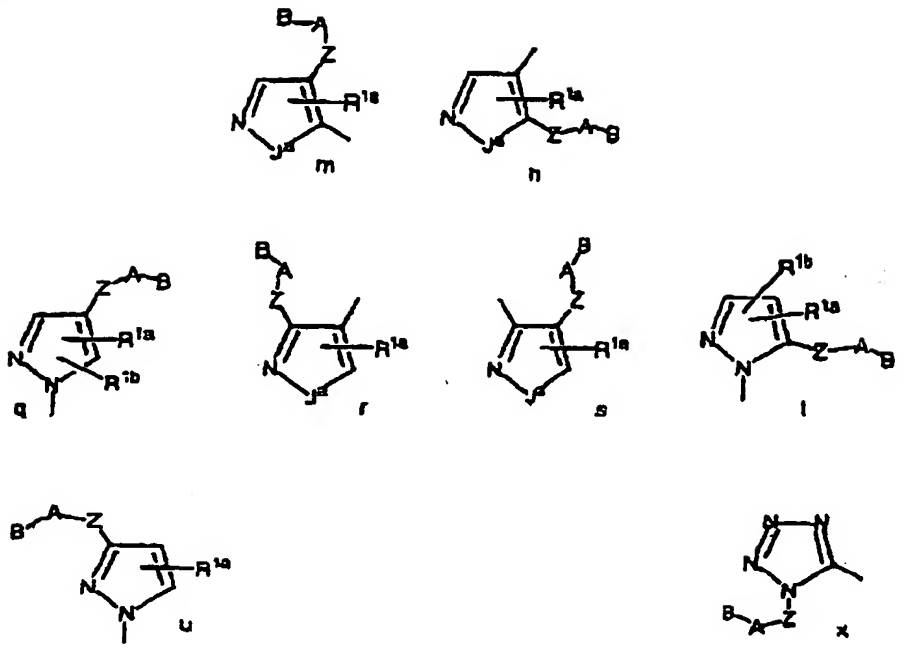

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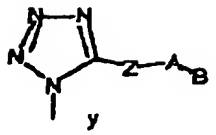


J^a est NH ou NR^{1a} ;

Z est choisi parmi alcoylène ayant de 1 à 4 atomes de carbone, $(CH_2)_rO(CH_2)_r$, $(CH_2)_rNR^3(CH_2)_r$, $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)O(CH_2)_r$; $(CH_2)_rOC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_rNR^3C(O)(CH_2)_r$, $(CH_2)_rOC(O)O(CH_2)_r$, $(CH_2)_rOC(O)NR^3(CH_2)_r$, $(CH_2)_rNR^3C(O)O(CH_2)_r$, $(CH_2)_rNR^3C(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, $(CH_2)_rSO_2NR^3(CH_2)_r$, $(CH_2)_rNR^3SO_2(CH_2)_r$ et $(CH_2)_rNR^3SO_2NR^3(CH_2)_r$, pourvu que Z ne forme pas une liaison N-N, N-O, N-S, NCH_2N, NCH_2O ou NCH_2S avec un cycle M ou un groupe A ;

R^{1a} et R^{1b} indépendamment sont absents ou sont choisis parmi $-(CH_2)_r-R^{1'}$, $-CH=CH-R^{1'}$, $NCH_2R^{1"}$, $OCH_2R^{1"}$, $SCH_2R^{1"}$, $NH(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$ et $S(CH_2)_2(CH_2)_tR^{1'}$;

en variante, R^{1a} et R^{1b}, lorsqu'ils sont fixés à des atomes de carbone voisins, forment, ensemble avec les atomes auxquels ils sont fixés, un cycle à 5 ou 8 chaînons saturé, partiellement saturé ou insaturé, substitué par de 0 à 2 R^4 et qui contient de 0 à 2 hétéroatomes choisis dans le groupe consistant en N, O et S ;

en variante, lorsque Z est C(O)NH et lorsque R^{1a} est fixé à un carbone cyclique voisin de Z, R^{1a} est un C(O) qui remplace l'hydrogène amide de Z pour former un imide cyclique ;

$R^{1'}$ est choisi parmi H, alcoyle ayant de 1 à 3 atomes de carbone, F, Cl, Br, I, -CN, -CHO, $(CF_2)_rCF_3$, $(CH_2)_rOR^2$, NR^2R^{2a}, $C(O)R^{2c}$, $OC(O)R^2$, $(CF_2)_rCO_2R^{2c}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $CH(=NR^{2c})NR^2R^{2a}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^{2b}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^{2a}R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$, $NR^2SO_2R^{2b}$, un radical carbocyclique ayant de 3 à 6 atomes de carbone substitué par de 0 à 2 R^4, et un système hétérocyclique ayant de 5 à 10 chaînons, contenant de 1 à 4 hétéroatomes choisis dans le groupe consistant en N, O et S et substitué par de 0 à 2 R^4 ;

$R^{1"}$ est choisi parmi H, $CH(CH_2OR^2)_2$, $C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $S(O)R^{2b}$, $S(O)_2R^{2b}$ et $SO_2NR^2R^{2a}$;

R^2, chaque fois qu'il apparaît, est choisi parmi H, CF_3, alcoyle ayant de 1 à 5 atomes de carbone, benzyle, un radical carbocyclique ayant de 3 à 6 atomes de carbone substitués par de 0 à 2 R^{4b}, et un système hétérocyclique ayant de 5 à 6 chaînons, contenant de 1 à 4 hétéroatomes choisis dans le groupe consistant en N, O et S

et substitué par de 0 à 2 R^{4b} ;

R^{2a}, chaque fois qu'il apparaît, est choisi parmi H, CF_3, alcoyle ayant de 1 à 6 atomes de carbone, benzyle, phénéthyle, un résidu carbocyclique ayant de 3 à 6 atomes de carbone substitués par de 0 à 2 R^{4b}, et un système hétérocyclique ayant de 5 à 6 chaînons et contenant de 1 à 4 hétéroatomes choisis dans le groupe consistant en N, O et S et substitué par de 0 à 2 R^{4b} ;

R^{2b}, chaque fois qu'il apparaît, est choisi parmi CF_3, alcoxy ayant de 1 à 4 atomes de carbone, alcoyle ayant de 1 à 6 atomes de carbone, benzyle, un résidu carbocyclique ayant de 3 à 6 atomes de carbone substitué par de 0 à 2 R^{4b}, et un système hétérocyclique ayant de 5 à 6 chaînons, contenant de 1 à 4 hétéroatomes choisis dans le groupe consistant en N, O et S et substitué par de 0 à 2 R^{4b} ;

R^{2c}, chaque fois qu'il apparaît, est choisi parmi CF_3, OH, alcoxy ayant de 1 à 4 atomes de carbone, alcoyle ayant de 1 à 6 atomes de carbone, benzyle, un résidu carbocyclique ayant de 3 à 6 atomes de carbone substitué par de 0 à 2 R^{4b}, et un système hétérocyclique ayant de 5 à 6 chaînons, contenant de 1 à 4 hétéroatomes choisis dans le groupe consistant en N, O et S et substitué par de 0 à 2 R^{4b};

en variante, R^2 et R^{2a} se combinent ensemble avec l'atome auquel ils sont fixés pour former un cycle à 5 ou 6 chaînons saturé, partiellement saturé ou insaturé, substitué par de 0 à 2 R^{4b} et contenant de 0 à 1 hétéroatome supplémentaire choisi dans le groupe consistant en N, O et S ;

R^3, chaque fois qu'il apparaît, est choisi parmi H, alcoyle ayant de 1 à 4 atomes de carbone et phényle ;

R^{3a}, chaque fois qu'il apparaît, est choisi parmi H, alcoyle ayant de 1 à 4 atomes de carbone et phényle ;

R^{3b}, chaque fois qu'il apparaît, est choisi parmi H, alcoyle ayant de 1 à 4 atomes de carbone et phényle;

R^{3c}, chaque fois qu'il apparaît, est choisi parmi alcoyle ayant de 1 à 4 atomes de carbone et phényle ;

A est choisi parmi :

un résidu carbocyclique ayant de 3 à 10 atomes de carbone substitués par de 0 à 2 R^4, et un système hétérocyclique ayant de 5 à 10 chaînons, contenant de 1 à 4 hétéroatomes choisis dans le groupe consistant en N, O et S et substitué par de 0 à 2 R^4 ;

B est choisi parmi : Y et X-Y ;

X est choisi parmi alcoylène ayant de 1 à 4 atomes de carbone, $-CR^2(CR^2R^{2b})(CH_2)=-$, $-C(O)-$, $-C(=NR^{1*})-$, $-CR^2(NR^{1*}R^2)-$, $-CR^2(OR^2)-$, $-CR^2(SR^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-S(O)_p-$, $-S(O)_pCR^2R^{2a}-$, $-CR^2R^{2a}S(O)_p-$, $-S(O)_2NR^2-$, $-NR^2S(O)_2-$, $-NR^2S(O)_2CR2R^{2a}-$, $-CR^2R^{2a}S(O)_2NR^2-$, $-NR^2S(O)_2NR^2-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)O-$, $-OC(O)NR^2-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$ et $-OCR^2R^{2a}-$;

Y est choisi parmi :

$(CH_2)_rNR^2R^{2a}$, pourvu que X-Y ne forment pas une liaison N-N, O-N ou S-N,

un résidu carbocyclique ayant de 3 à 10 atomes de carbone substitué par de 0 à 2 R^{4a}, et

un système hétérocyclique ayant de 5 à 10 chaînons, contenant de 1 à 4 hétéroatomes choisis dans le groupe consistant en N, O et S et substitué par de 0 à 2 R^{4a} ;

R^4, chaque fois qu'il apparaît, est choisi parmi H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, alcoyle ayant de 1 à 4 atomes de carbone, -CN, NO_2,

$(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$, $CH(=NS(O)_2R^5)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $C(O)NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-alcoyle ayant de 1 à 4 atomes de carbone, $NR^2SO_2R^5$, $S(O)_pR^5$, $(CF_2)_rCF_3$, NCH_2R^{1*}, OCH_2R^{1*}, SCH_2R^{1*}, $N(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$ et $S(CH_2)_2(CH_2)_tR^{1'}$,

en variante, l'un de R^4 est un hétérocycle aromatique ayant de 5 à 6 chaînons et contenant de 1 à 4 hétéroatomes choisis dans le groupe consistant en N, O et S ;

R^{4a}, chaque fois qu'il apparaît, est choisi parmi H, =O, $(CH_2)_rOR^2$, $(CH_2)_r$-F, $(CH_2)_r$-Br, $(CH_2)_r$-Cl, I, alcoyle ayant de 1 à 4 atomes de carbone, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)rNR^2R^{2b}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-alcoyle ayant de 1 à 4 atomes de carbone dans la partie alcoyle, $C(O)NHSO_2$-alcoyle ayant de 1 à 4 atomes de carbone dans la partie alcoyle, $NR^2SO_2R^5$, $S(O)_pR^5$ et $(CF_2)_rCF_3$;

en variante, l'un de R^{4a} est un hétérocycle aromatique ayant de 5 à 6 chaînons et contenant de 1 à 4 hétéroatomes choisis dans le groupe consistant en N, O et S et substitué par de 0 à 1 R^5 ;

R^{4b}, chaque fois qu'il apparaît, est choisi parmi H, =O, $(CH_2)_rCR^3$, F, Cl, Br, I, alcoyle ayant de 1 à 4 atomes de carbone, -CN, NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)$

NR^3R^{3a}, $CH(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, NR^3SO_2-alcoyle ayant de 1 à 4 atomes de carbone dans la partie alcoyle, $NR^3SO_2CF_3$, NR^3SO_2-phényle, $S(O)_pCF_3$, $S(O)_p$-alcoyle ayant de 1 à 4 atomes de carbone, $S(O)_p$-phényle et $(CF_2)_rCF_3$;

R^5, chaque fois qu'il apparaît, est choisi parmi CF_3, alcoyle ayant de 1 à 6 atomes de carbone, phényle substitué par de 0 à 2 R^6 et benzyle substitué par de 0 à 2 R^6 ;

R^6, chaque fois qu'il apparaît, est choisi parmi H, OH, $(CH_2)_rOR^2$, F, Cl, Br, I, alcoyle ayant de 1 à 4 atomes de carbone, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$ et NR^2SO_2alcoyle ayant de 1 à 4 atomes de carbone dans la partie alcoyle ;

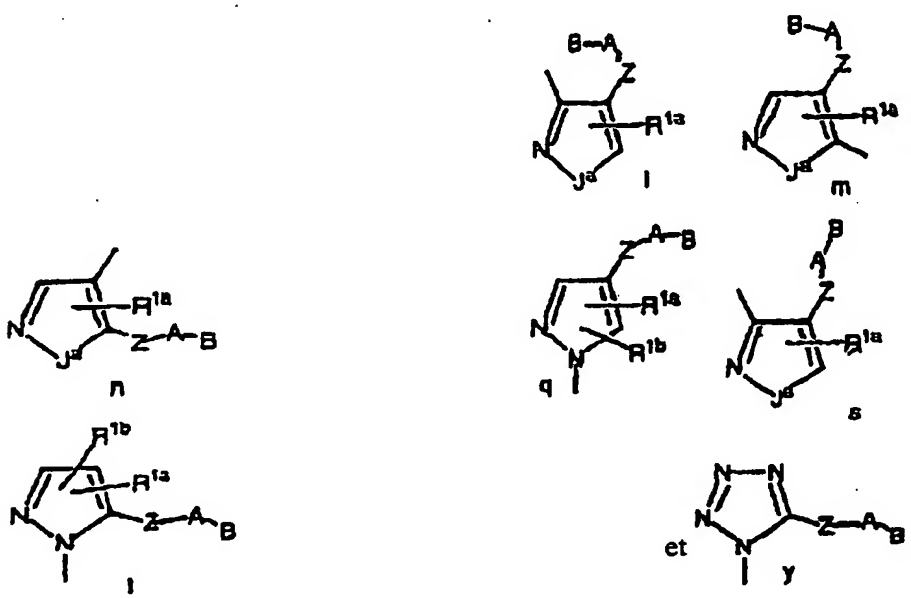
p est choisi parmi 0, 1 et 2 ;

r est choisi parmi 0, 1, 2 et 3 ;

et

t est choisi parmi 0 et 1.

2. Composé suivant la revendication 1, dans lequel M est choisi dans le groupe :

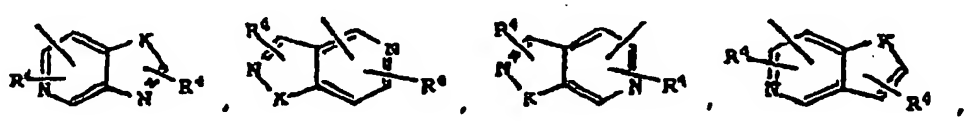


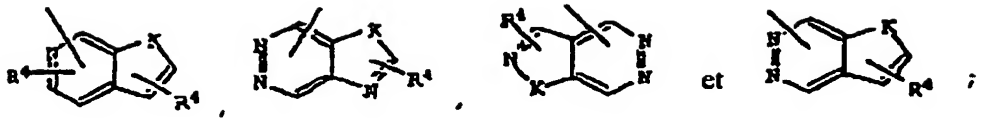
Z est choisi parmi $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)O(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$ et $(CH_2)_rSO_2NR^3(CH_2)_r$; et

Y est choisi parmi l'un des systèmes carbocycliques et hétérocycliques suivants qui sont substitués par de 0 à 2 R^{4a} ;

phényle, pipéridinyle, pipérazinyle, pyridyle, pyrimidyle, furanyle, morpholinyle, thiophényle, pyrrolyle, pyrrolidinyle, oxazolyle, isoxazolyle, thiazoyle, isothiazolyle, pyrazolyle, imidazolyle, oxadiazote, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazote, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, benzofurane, benzothiofurane, indole, benzimidazole, benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole et isoindazole ;

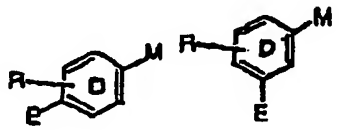
Y peut aussi être choisi parmi les systèmes cycliques hétéroaryliques bicycliques suivants :





K est choisi parmi O, S, NH et N.

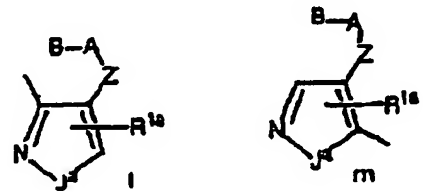
3. Composé suivant la revendication 2, dans lequel le composé répond à la formule Ia ou Ib :



Ia Ib

dans lesquelles:

le cycle D est phényle ou pyridyle ;
E est choisi parmi F, Cl, Br et alcoxy ayant de 1 à 3 atomes de carbone ;
R est choisi parmi H, F, Cl, Br, OR^3 et CH_2OR^3 ;
M est choisi dans le groups ;



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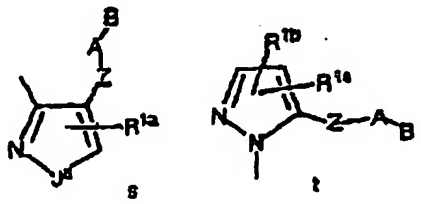

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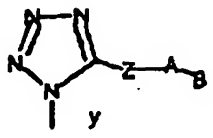


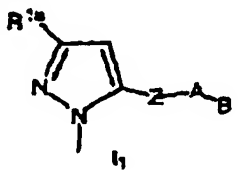
y

Z est choisi parmi $(CH_2)_rC(O)(CH_2)_r$ et $(CH_2)_rC(O)NR^3(CH_2)_r$; et
Y est choisi parmi l'un des systèmes carbocycliques et hétérocycliques suivants qui sont substitués par de 0 à 2 R^{4a} ;
phényle, pipéridinyle, pipérazinyle, pyridyle, pyrimidyle, furanyle, morpholinyle, thiophényle, pyrrolyle, pyrro-

lidinyle, oxazolyle, isoxazolyle, thiazolyle, isothiazolyle, pyrazolyle, imidazolyle, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, benzofurane, benzothiofurane, indole, benzimidazole, benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole et isoindazole.

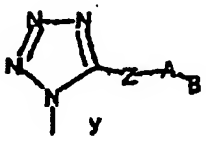
4. Composé suivant la revendication 3, dans lequel :

le cycle D est phényle ;
E est choisi parmi F, Cl, Br et OCH_3 ;
R est choisi parmi H, F, Cl et Br ;
M est choisi dans le groupe :



I_1

et



y

A est choisi parmi :

un radical carbocyclique ayant de 5 à 6 atomes de carbone substitués par de 0 à 2 R^4, et
un système hétérocyclique ayant de 5 à 6 chaînons contenant de 1 à 4 hétéroatomes choisis dans le groupe consistant en N, O et S substitués par de 0 à 2 R^4 ;

Y est choisi parmi l'un des systèmes carbocycliques et hétérocycliques suivants qui sont substitués par de 0 à 2 R^{4a} ;
phényle, pipéridinyle, pipérazinyle, pyridyle, pyrimidyle, furanyle, morpholinyle, thiophényle, pyrrolyle, pyrrolidinyle, oxazolyle, isoxazolyle, thiazolyle, isothiazolyle, pyrazolyle, imidazolyle, benzimidazolyle, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazote et 1,3,4-triazole ;
R^2, chaque fois qu'il apparaît, est choisi parmi H, CF_3, alcoyle ayant de 1 à 5 atomes de carbone, benzyle, un radical carbocyclique ayant de 3 à 6 atomes de carbone substitué par de 0 à 2 R^{4b}, et un système hétérocyclique ayant de 5 à 6 chaînons, contenant de 1 à 4 hétéroatomes choisis dans le groupe consistant en N, O et S et substitué par de 0 à 2 R^{4b} ;
R^{2a}, chaque fois qu'il apparaît, est choisi parmi H, CF_3, alcoyle ayant de 1 à 6 atomes de carbone, benzyle, phénéthyle, un résidu carbocyclique ayant de 5 à 6 atomes de carbone substitué par de 0 à 2 R^{4b}, et un système hétérocyclique ayant de 5 à 6 chaînons, contenant de 1 à 4 hétéroatomes choisis dans le groupe consistant en N, O et S et substitué par de 0 à 2 R^{4b} ;
R^{2b}, chaque fois qu'il apparaît, est choisi parmi CF_3, alcoxy ayant de 1 à 4 atomes de carbone, alcoyle ayant de 1 à 5 atomes de carbone, benzyle, un résidu carbocyclique ayant de 5 à 6 atomes de carbone substitué par de 0 à 2 R^{4b}, et un système hétérocyclique ayant de 5 à 6 chaînons, contenant de 1 à 4 hétéroatomes choisis dans le groupe consistant en N, O et S substitué par de 0 à 2 R^{4b} ;
R^{2c}, chaque fois qu'il apparaît, est choisi parmi CF_3, OH, alcoxy ayant de 1 à 4 atomes de carbone, alcoyle ayant de 1 à 6 atomes de carbone, benzyle, un résidu carbocyclique ayant de 5 à 6 atomes de carbone

substitué par de 0 à 2 R^{4b}, et un système hétérocyclique ayant de 5 à 6 chaînons ; contenant de 1 à 4 hétéroatomes choisis dans le groupe consistant en N, O et S substitué par de 0 à 2 R^{4b} ;
en variante, R^2 et R^{2a} se combinent ensemble avec l'atome auquel ils sont fixés pour former un cycle choisi parmi imidazolyle, morpholino, pipérazinyle, pyridyle et pyrrolidinyle, substitué par de 0 à 2 R^{4b} ;
R^4, chaque fois qu'il apparaît, est choisi parmi H, =O, OR^2, CH_2OR^2, F, Cl, alcoyle ayant de 1 à 4 atomes de carbone, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$, $CH(=NS(O)_2R^5)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, NR^2SO_2-alcoyle ayant de 1 à 4 atomes de carbone dans la partie alcoyle, $S(O)_2R^5$ et CF_3
pourvu que si B est H, R^4 soit autre que tétrazole, C(O)-alcoxy et $C(O)NR^2R^{2a}$;
R^{4a}, chaque fois qu'il apparaît, est choisi parmi H, =O, $(CH_2)_rOR^2$, F, Cl, alcoyle ayant de 1 à 4 atomes de carbone, NR^2R^{2a}, $CH_2NR^2R^{2a}$, NR^2R^{2b}, $CH_2NR^2R^{2b}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_2R^5$ et CF_3 ; et
R^{4b}, chaque fois qu'il apparaît, est choisi parmi H, =O, $(CH_2)_rOR^3$, F, Cl, alcoyle ayant de 1 à 4 atomes de carbone, NR^3R^{3a}, $CH_2NR^3R^{3a}$, $C(O)R^3$, $CH_2O(O)R^3$, $C(O)OR^{3c}$, $C(O)NR^3R^{3a}$, $CH(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, NR^3SO_2-alcoyle ayant de 1 à 4 atomes de carbone dans la partie alcoyle, $NR^3SO_2CF_3$, NR^3SO_2-phényle, $S(O)_2CF_3$, $S(O)_2$-alcoyle ayant de 1 à 4 atomes de carbone, $S(O)_2$-phényle et CF_3.

5. Composé suivant la revendication 1, dans lequel le composé est choisi parmi :

le 3-méthyl-1-(2-méthoxy)phényl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 3-méthyl-1-(3-méthoxy)phényl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 3-méthyl-1-(4-méthoxy)phényl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 3-méthyl-1-(2-hydroxy)phényl-1H-pyrazote-5-(N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 3-méthyl-1-(3-hydroxy)phényl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 3-méthyl-1-(4-hydroxy)phényl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 3-méthyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(3-fluoro-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 3-méthyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(3-bromo-4-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 3-méthyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(3-iodo-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 3-méthyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(3-méthyl-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 3-méthyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(4-N-carboxydiméthylamine)phényl)carboxyamide ;
le 3-méthyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(4-N-pyrrolidinocarbonyl)phényl)carboxyamide ;
le 3-méthyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(4-a-méthyl-N-pyrrolidino)phényl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(4-N-pyrrolidinocarbonyl)phényl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(5-(2-méthanesulfonyl)phényl)pyridine-2-yl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(5-N-pyrrolidinocarbonyl)pyridine-2-yl)carboxyamide ;
le 3-méthyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(5-N-pyrrolidinocarbonyl)pyridine-2-yl)carboxyamide ;
le 3-méthyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(5-(2-sulfonamido)phényl)pyridine-2-yl)carboxyamide ;
le 3-méthyl-1-(4-méthoxyphényl)-1H-pyrazole-5-N-(4-(N-carboxyl-3-hydroxypyrrolidino)phényl)carboxyamide ;
le 1-(4-méthoxyphényl)-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)aminocarbonyl]tétrazole ;
le 3-méthyl-1-(4-méthoxy-3-chloro)phényl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 3-méthyl-1-(4-trifluorométhoxy)phényl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-(3-bromophényl)-3-méthyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-(3-iodophényl)-3-méthyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-(3,4-méthylènedioxanephényl)-3-méthyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-(4-méthoxyphényl)-3-hydroxylméthylène-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide ;
le 1-(4-méthoxyphényl)-3-formaldéhyde-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide ;
le 1-(4-méthoxyphényl)-3-méthylcarboxylate-1H-pyrazole-5-(4'-pyrrolidinocarbonyl)anilide ;
le 1-(4'-chlorophényl)-3-méthyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-(4'-chlorophényl)-3-méthyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1-pyridyl-1'-phényl]-4-yl)carboxyamide ;

le 1-(3',4'dichlorophényl)-3-méthyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1-1']-biphène-4-yl)carboxyamide ;
le 1-(3'-chlorophényl)-3-méthyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1-1']-biphène-4-yl)carboxyamide ;
le N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)-1-(4-méthoxyphényl)-3-(méthylthio)pyrazole-5-carboxamide ;
le 1-(4-méthoxyphényl)-3-(méthylsulfonyl)-N-(5-(2'-méthylsulfonylphényl)pyrimide-2-yl)pyrazole-5-carboxamide ;
le N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)-1-(4-méthoxyphényl)-3-(méthylsulfonyl)-1H-pyrazole-5-carboxamide ;
le N-(4-benzoylpyrrolidino)-1-(4-méthoxyphényl)-3-(méthylthio)-1H-pyrazole-5-carboxamide ;
le 1-(4-méthoxyphényl)-N-(5-(2'-méthylsulfonylphényl)pyrimide-2-yl)-3-(méthylthio)-1H-pyrazole-5-carboxamide ;
le N-(4-benzoylpyrrolidino)-1-(4-méthoxyphényl)-3-(méthylsulfonyl)-1H-pyrazole-5-carboxamide ;
le N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)-1-(4-méthoxyphényl)-3-(méthoxyméthyl)-1H-pyrazole-5-carboxamide ;
le N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)-1-(4-méthoxyphényl)-3-carbométhoxy-1H-pyrazole-5-carboxamide ;
le N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)-1-(4-méthoxyphényl)-3-(méthylsulfonylméthyl)-1H-pyrazole-5-carboxamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(5-(2-méthanesulfonyl)phényl)pyrimidine-2-yl) carboxyamide ;
le 3-méthyl-1-(4-méthoxyphényl)-1H-pyrazole-5-N-(4-(N-carboxyl-2-carbométhoxypyrrolidino)phényl)carboxyamide ;
le 3-méthyl-1-(4-méthoxyphényl)-1H-pyrazole-5-N-(4-(N-carboxyl-3-aminopyrrolidino)phényl)carboxyamide ;
le 3-méthyl-1-(4-méthoxyphényl)-1H-pyrazole-5-N-(4-(N-carboxyl-3-méthoxypyrrolidino)phényl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(5-(2-aminosulfonyl)phényl)pyridine-2-yl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(4-amidino)phényl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(4-(N-pyrrolidino)formylimino)phényl)carboxyamide ;
la 3-trifluorométhyl-5-(N-(2'-aminosulfonyl-1,1']-biphène-4-yl)-1-(4-méthoxyphényl)pyrrolo[3,4-d]pyrazole-4,6-(1H,5H)-dione ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-carbométhoxy-(N-(2'-aminosulfonyl-[1,1']-biphène-4-yl))carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-hydroxyméthyl-(N-(2'-aminosulfonyl-[1,1']-biphène-4-yl))carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-2-fluoro(4-(N-pyrrolidino)formylimino)phényl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(4-(N-pyrrolidino)formyl-N-[(2-propyl]méthylcarbamoyl)imino)phényl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1 H-pyrazole-5-(N-(4-(N-pyrrolidino)formyl-N-(méthanesulfamoyl) imino)phényl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-((4-amidino)phényl)méthyl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-((4-(N-pyrrolidino)formylimino)phényl)méthyl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-((1-benzyl)pipéridine-4-yl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-((1-(pyridine-2-yl)méthyl)pipéridine-4-yl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(4-(2-méthylimidazo-1-yl))phényl)carboxyamide ;
le 3-méthyl-(4-méthoxy)phényl-1H-pyrazole-5-(N-{4-(5-méthylimidazole-1-yl}phényl)carboxyamide ;
le 3-méthyl-(4-méthoxy)phényl-1H-pyrazole-5-(N-{4-(4-méthylimidazole-1-yl}phényl)carboxyamide ;
le 3-trifluorométhyl-(4-méthoxy)phényl-1H-pyrazofe-5-(N-{4-(5-carbométhoxy-imidazole-1-yl}phényl)carboxyamide ;
le 3-trifluorométhyl-(4-méthoxy)phényl-1H-pyrazole-5-(N-{4-(5-carboxy-imidazole-1-yl}phényl)carboxyamide ;
le 1-(4'-méthoxyphényl)-3-hydroxylméthyl-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phényl)carboxyamide ;
le 1-(4'-méthoxyphényl)-3-formaldéhyde-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phényl)carboxyamide ;
l'acide 1-(4'-méthoxyphényl)-5-N-(4'-(pyrrolidinocarbonyl)anilide)-1H-pyrazol-3-yl-carboxylique ;
le 1-(4'-méthoxyphényl)-3-méthylcarboxylate-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phényl)carboxyamide ;
le 1-(4'-méthoxyphényl)-3-cyanométhyl-1H-pyrazole-5-N-(4'-pyrrolidinocarbonyl)phényl)carboxyamide ;

l'acide 2-(1'-(4"-méthoxyphényl)-5'-(4"-pyrrolidinyl-one)anilide-1H-pyrazol-3'-yl)acétique ;
le 1-(4'-méthoxyphényl)-3-bromométhyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphène-4-yl))carboxyamide ;
le 1-(4'-méthoxyphényl)-3-aminométhyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-(4'-méthoxyphényl)-3-(N-méthylsulfonylamino)méthyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-(4'-méthoxyphényl)-3-(imidazole-1-yl)méthyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-(4'-méthoxyphényl)-3-hydroxyméthyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-(4'-méthoxyphényl)-3-trifluoroacétylhydroxyméthyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-(4'-méthoxy-2'-méthoxycarbonylphényl)-3-trifluorométhyl-1H-pyrazole-5-N-(2'-méthylsulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-(4'-méthoxy-2'-hydroxycarbonylphényl)-3-trifluorométhyl-1H-pyrazole-5-N-(2'-méthylsulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-(4'-méthoxy-2'-méthoxycarbonylphényl)-3-trifluorométhyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-(4'-méthoxy-2'-hydroxycarbonylphényl)-3-trifluorométhyl-1H-pyrazole-5-N-(2'-tert-butylaminosulfonyl-[1,1']-biphényl)carboxyamide ;
le 1-(4'-méthoxy-2'-hydroxycarbonylphényl)-3-trifluorométhyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-(4'-méthoxy-2'-hydroxylméthylphényl)-3-trifluorométhyl-1H-pyrazole-5-N-(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-(4'-méthoxyphényl)-3-méthyl-1H-pyrazole-5-N-(4'-(3"-méthyl-3"-pyrazoline-5"-one-2"-yl)phényl) carboxyamide ;
le 1-(4'-méthoxyphényl)-3-méthyl-1H-pyrazole-5-N-(4'-(6"-méthylbenzothiazol-2"-yl)phényl)carboxyamide ;
le 1-(4'-méthoxyphényl)-3-méthyl-1H-pyrazole-5-N-(4'-(4"-méthylpipéridino)phényl)carboxyamide ;
le 1-(4'-méthoxyphényl)-3-méthyl-1H-pyrazole-5-N-(4'-(2"-méthylimidazole-1"-yl)phényl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(4-carboxy(N-méthylimidazo-2-yl)phényl)carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(4-hydroxyméthyl(2-(imidazole-2-yl)phényl)))carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(4-hydroxyméthyl(2-(1-benzyl-imidazole-2-yl) phényl)))carboxyamide ;
le 1-(4-méthoxyphényl)-3-trifluorométhyl-1H-pyrazole-5-(N-(4-(2-carboxy(imidazole-2-yl)phényl)))carboxyamide ;
le 3-trifluorométhyl-1-(4-méthoxyphényl)-1H-pyrazole-5-(N-(4-(N-(4-méthoxyphényl)amino-(2-thiazolyl)méthyl)phényl)))carboxyamide ;
le 1-(4-méthoxyphényl)-3-trifluorométhyl-1H-pyrazole-5-(N-(4-(2-carboxy-(4,5-dihydrothiazol-2-yl)phényl))) carboxyamide ;
le 1-(4-méthoxyphényl)-3-trifluorométhyl-1H-pyrazole-5-N-4-(2-(4',5'-dihydro-1'-H-imidazote-2'-yl)phényl) carboxyamide ;
le 1-(4-méthoxyphényl)-3-trifluorométhyl-1H-pyrazole-5-[4-(1,4,5,6-tétrahydro-pyrimide-2-yl)-phényl]carboxyamide ;
le 1-(4-méthoxyphényl)-3-trifluorométhyl-1H-pyrazole-5-[4-(N-méthyl-4,5,6-trihydro-pyrimide-2-yl)-phényl] carboxyamide ;
le 1-(4-méthoxyphényl)-3-trifluorométhyl-1H-pyrazole-5-N-1-(2-fluoro-4-imidazolinephényl)carboxyamide ;
le 1-(4-méthoxyphényl)-3-trifluorométhyl-1H-pyrazole-5-N-1-(2-fluoro-4-N-méthylimidazolinephényl)carboxyamide ;
le 1-(4-méthoxyphényl)-3-trifluorométhyl-1H-pyrazole-5-N-[4-(4,5-dihydro-1-N-méthyl-imidazo-2-yl)phényl] carboxyamide ;
le 1-(4-méthoxyphényl)-3-trifluorométhyl-1H-pyrazole-5-N-[4-(pyrimidine-2-yl)phényl]carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-(éthoxycarbonyl)-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phényl]carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-(carboxyamide)-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phényl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[(2-hydroxyéthyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phényl)carboxyamide ;
l'acide 1-[(4-méthoxy)phényl)-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phényl)carboxyamide-3-hydroxamique ;

le 1-[(4-méthoxy)phényl]-3-[phénylcarboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phényl]carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[(3-hydroxypropyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phényl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[méthylcarboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phényl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[(benzyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phényl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[(diméthyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phényl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[(phényléthyl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phényl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[(2-hydroxyphényl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phényl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[(3-hydroxyphényl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phényl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[(4-hydroxyphényl)carboxyamide]-1H-pyrazole-5-[(4-(N-pyrrolidinocarbonyl)phényl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[(méthoxycarbonyl)amino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-amino-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[(méthoxycarbonyl)méthylamino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[(2-hydroxy)éthylamino]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[E-2-(méthoxycarbonyl)éthényl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[2-(méthoxycarbonyl)éthyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[E-2-(carboxy)éthényl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[2-(carboxy)éthyl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[E-2-(carboxyamide)éthényl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-[E-2-(hydroxyméthyl)éthényl]-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-(3-hydroxypropyl)-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-propyl-1H-pyrazole-5-[(2'-aminosulfonyl-[1,1']-biphène-4-yl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-(trifluorométhyl)-4-cyano-1H-pyrazole-5-[(2'-méthylsulfonyl-3-fluoro-[1,1']-biphène-4-yl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-(trifluorométhyl)-4-(amidino)-1H-pyrazole-5-((2'méthylsulfonyl-3-fluoro-[1,1']-biphène-4-yl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-(trifluorométhyl)-4-(N-hydroxyamidino)-1H-pyrazole-5-[(2'méthylsulfonyl-3-fluoro-[1,1']-biphène-4-yl)carboxyamide ;
le 1-[(4-méthoxy)phényl]-3-(trifluorométhyl)-4-(éthoxycarbonyl)-1H-pyrazole-5-[(2'méthylsulfonyl-3-fluoro-[1,1']-biphène-4-yl)carboxyamide ; et
l'acide 1-[(4-méthoxy)phényl]-3-(trifluorométhyl)-1H-pyrazole-5-[(2'méthylsulfonyl-3-fluoro-[1,1']-biphène-4-yl)carboxyamide-4-carboxylique ;

et leurs sels acceptables pharmaceutiquement.

6. Composition pharmaceutique comprenant: un véhicule acceptable pharmaceutiquement et une quantité efficace thérapeutiquement d'un composé selon l'une des revendications 1 à 5 ou de l'un de ses sels acceptables pharmaceutiquement.

7. Un composé suivant l'une des revendications 1 à 5 ou l'un de ses sels acceptables pharmaceutiquement à utiliser

en thérapeutique.

8. Utilisation d'un composé suivant l'une des revendications 1 à 5 ou de l'un de ses sels acceptables pharmaceutiquement pour la fabrication d'un médicament pour le traitement d'un trouble thromboembolique.